Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacological therapies for management of opium withdrawal (Review)

Rahimi-Movaghar A, Gholami J, Amato L, Hoseinie L, Yousefi-Nooraie R, Amin-Esmaeili M

Rahimi-Movaghar A, Gholami J, Amato L, Hoseinie L, Yousefi-Nooraie R, Amin-Esmaeili M.
Pharmacological therapies for management of opium withdrawal.
Cochrane Database of Systematic Reviews 2018, Issue 6. Art. No.: CD007522.
DOI: 10.1002/14651858.CD007522.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Pharmacological therapies for management of opium withdrawal

Afarin Rahimi-Movaghar[1], Jaleh Gholami[1], Laura Amato[2], Leila Hoseinie[1], Reza Yousefi-Nooraie[3], Masoumeh Amin-Esmaeili[1]

[1]Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran. [2]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy. [3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada

Contact address: Afarin Rahimi-Movaghar, Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, No. 486, South Karegar Ave., Tehran, Tehran, 1336616357, Iran. rahimia@tums.ac.ir.

Editorial group: Cochrane Drugs and Alcohol Group.
Publication status and date: New, published in Issue 6, 2018.

Citation: Rahimi-Movaghar A, Gholami J, Amato L, Hoseinie L, Yousefi-Nooraie R, Amin-Esmaeili M. Pharmacological therapies for management of opium withdrawal. *Cochrane Database of Systematic Reviews* 2018, Issue 6. Art. No.: CD007522. DOI: 10.1002/14651858.CD007522.pub2.

ABSTRACT

Background

Pharmacologic therapies for management of heroin withdrawal have been studied and reviewed widely. Opium dependence is generally associated with less severe dependence and milder withdrawal symptoms than heroin. The evidence on withdrawal management of heroin might therefore not be exactly applicable for opium.

Objectives

To assess the effectiveness and safety of various pharmacologic therapies for the management of the acute phase of opium withdrawal.

Search methods

We searched the following sources up to September 2017: CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, regional and national databases (IMEMR, Iranmedex, and IranPsych), main electronic sources of ongoing trials, and reference lists of all relevant papers. In addition, we contacted known investigators to obtain missing data or incomplete trials.

Selection criteria

Controlled clinical trials and randomised controlled trials on pharmacological therapies, compared with no intervention, placebo, other pharmacologic treatments, different doses of the same drug, and psychosocial intervention, to manage acute withdrawal from opium in a maximum duration of 30 days.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane.

Main results

We included 13 trials involving 1096 participants. No pooled analysis was possible. Studies were carried out in three countries, Iran, India, and Thailand, in outpatient and inpatient settings. The quality of the evidence was generally very low.

When the mean of withdrawal symptoms was provided for several days, we mainly focused on day 3. The reason for this was that the highest severity of opium withdrawal is in the second to fourth day.

Comparing different pharmacological treatments with each other, clonidine was twice as good as methadone for completion of treatment (risk ratio (RR) 2.01, 95% confidence interval (CI) 1.69 to 2.38; 361 participants, 1 study, low-quality evidence). All the other results showed

no differences between the considered drugs: baclofen versus clonidine (RR 1.06, 95% CI 0.63 to 1.80; 66 participants, 1 study, very low-quality evidence); clonidine versus clonidine plus amantadine (RR 1.03, 95% CI 0.86 to 1.24; 69 participants, 1 study); clonidine versus buprenorphine in an inpatient setting (RR 1.04, 95% CI 0.90 to 1.20; 1 study, 35 participants, very low-quality evidence); methadone versus tramadol (RR 0.95, 95% CI 0.65 to 1.37; 1 study, 72 participants, very low-quality evidence); methadone versus methadone plus gabapentin (RR 1.17, 95% CI 0.96 to 1.43; 1 study, 40 participants, low-quality evidence), and tincture of opium versus methadone (1 study, 74 participants, low-quality evidence).

Comparing different pharmacological treatments with each other, adding amantadine to clonidine decreased withdrawal scores rated at day 3 (mean difference (MD) -3.56, 95% CI -5.97 to -1.15; 1 study, 60 participants, very low-quality evidence). Comparing clonidine with buprenorphine in an inpatient setting, we found no difference in withdrawal symptoms rated by a physician (MD -1.40, 95% CI -2.93 to 0.13; 1 study, 34 participants, very low-quality evidence), and results in favour of buprenorpine when rated by participants (MD -11.80, 95% CI -15.56 to -8.04). Buprenorphine was superior to clonidine in controlling severe withdrawal symptoms in an outpatient setting (RR 0.35, 95% CI 0.19 to 0.64; 1 study, 76 participants). We found no difference in the comparison of methadone versus tramadol (MD 0.04, 95% CI -2.68 to 2.76; 1 study, 72 participants) and in the comparison of methadone versus methadone plus gabapentin (MD -2.20, 95% CI -6.72 to 2.32; 1 study, 40 participants).

Comparing clonidine versus buprenorphine in an outpatient setting, more adverse effects were reported in the clonidine group (1 study, 76 participants). Higher numbers of participants in the clonidine group experienced hypotension at days 5 to 8, headache at days 1 to 8, sedation at days 5 to 8, dizziness and dry mouth at days 1 to 10, and nausea at days 1 to 9. Sweating was reported in a significantly higher number of participants in the buprenorphine group at days 1 to 10. We found no difference between groups for all the other comparisons considering this outcome.

Comparing different dosages of the same pharmacological detoxification treatment, a high dose of clonidine (1 to 1.2 mg/day) did not differ from a low dose of clonidine (0.5 to 0.6 mg/day) in completion of treatment in an inpatient setting (RR 1.00, 95% CI 0.84 to 1.19; 1 study, 68 participants), however a higher number of participants with hypotension was reported in the high-dose group (RR 3.25, 95% CI 1.77 to 5.98). Gradual reduction of methadone was associated with more adverse effects than abrupt withdrawal of methadone (RR 2.25, 95% CI 1.02 to 4.94; 1 study, 20 participants, very low-quality evidence).

Authors' conclusions

Results did not support using any specific pharmacological approach for the management of opium withdrawal due to generally very low-quality evidence and small or no differences between treatments. However, it seems that opium withdrawal symptoms are significant, especially at days 2 to 4 after discontinuation of opium. All of the assessed medications might be useful in alleviating symptoms. Those who receive clonidine might experience hypotension.

PLAIN LANGUAGE SUMMARY

Medications for the management of opium withdrawal

What was the aim of this review?

The aim of this Cochrane Review was to find out which medications are more effective and safer for the management of opium withdrawal. We collected and analysed all relevant studies to answer this question, and found 13 studies involving 1096 participants.

Key messages

This review included the following 12 comparisons: baclofen versus clonidine, clonidine versus clonidine plus amantadine, clonidine versus buprenorphine, high-dose clonidine versus low-dose clonidine versus symptomatic management, clonidine versus methadone, methadone versus tramadol, methadone versus methadone plus gabapentin, gradual reduction of methadone versus sudden withdrawal of methadone, methadone plus amitriptyline versus methadone, diphenoxylate versus propoxyphene, three different protocols of tincture of opium, and tincture of opium versus methadone. The studies were carried out in three countries, Iran, India, and Thailand. Support from a pharmaceutical company in the form of free provision of medications was reported in only one study.

The evidence is unclear as to whether any of the evaluated medications is more effective than another in the management of opium withdrawal. However, it seems that opium withdrawal symptoms are significant in the first days after discontinuation of opium. All of the assessed medications might be useful in alleviating symptoms. Use of clonidine might result in low blood pressure.

What was studied in this review?

Withdrawal symptoms from opium are similar to those of other opioids such as heroin, but with mild intensity. Patients usually need medications to help alleviate withdrawal symptoms.

What are the main results of the review?

We are uncertain as to whether the effects of clonidine differ from those of baclofen in number of participants who completed treatment (certainty of evidence was very low).

We are uncertain as to whether adding amantadine to clonidine decreases the severity of withdrawal symptoms in days 1 to 3 in an inpatient setting, or whether it has an effect on completion of treatment (certainty of evidence was very low).

We are uncertain as to whether buprenorphine is better than clonidine in controlling withdrawal symptoms in both inpatient and outpatient settings (certainty of evidence was very low). Adverse effects, including hypotension, were reported in higher numbers in the clonidine group.

We are uncertain as to whether a high dose of clonidine differs from a low dose of clonidine in completion of treatment in an inpatient setting (certainty of evidence was very low), however a higher number of cases of low blood pressure was reported with high-dose clonidine.

Clonidine may be better than methadone in keeping patients in treatment in an outpatient setting.

We are uncertain as to whether tramadol differs from methadone in completion of treatment and in alleviating withdrawal symptoms, and whether adverse effects are common with methadone (certainty of evidence was very low).

Adding gabapentin to methadone may make little or no difference in completion of treatment and the severity of withdrawal symptoms.

We are uncertain as to whether abrupt withdrawal of methadone is associated with fewer patient complaints than gradual reduction of methadone (certainty of evidence was very low).

Tincture of opium may make no difference in completion of treatment, severity of withdrawal symptoms, and adverse effects in comparison to methadone.

How up-to-date is this review?

We searched for studies published up to September 2017.

Summary of findings for the main comparison. Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal

Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal

Patient or population: management of opium withdrawal
Setting: outpatient and inpatient
Intervention: pharmacological detoxification treatment
Comparison: other pharmacological detoxification treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other pharmacological detoxification treatment	Risk with pharmacological detoxification treatment				
Completion of treatment: baclofen versus clonidine	Study population 441 per 1000	468 per 1000 (278 to 794)	RR 1.06 (0.63 to 1.80)	66 (1 CCT)	⊕⊖⊖⊖ VERY LOW [1 2]	
Completion of treatment: clonidine versus clonidine plus amantadine, inpatient setting	Study population 857 per 1000	883 per 1000 (737 to 1000)	RR 1.03 (0.86 to 1.24)	69 (1 CCT)	⊕⊖⊖⊖ VERY LOW [2 3]	
Completion of treatment: clonidine versus buprenorphine, inpatient setting	Study population 952 per 1000	990 per 1000 (857 to 1000)	RR 1.04 (0.90 to 1.20)	35 (1 CCT)	⊕⊖⊖⊖ VERY LOW [2 4]	
Completion of treatment: clonidine versus methadone	Study population 415 per 1000	834 per 1000 (701 to 988)	RR 2.01 (1.69 to 2.38)	361 (1 CCT)	⊕⊕⊖⊖ LOW [5]	
Completion of treatment: methadone versus tramadol	Study population 629 per 1000	597 per 1000 (409 to 861)	RR 0.95 (0.65 to 1.37)	72 (1 CCT)	⊕⊖⊖⊖ VERY LOW [2 6]	

Completion of treatment: methadone versus methadone plus gabapentin	Study population		RR 1.17 (0.96 to 1.43)	40 (1 RCT)	⊕⊕⊖⊖ LOW [2]
	850 per 1000	994 per 1000 (816 to 1000)			
Completion of treatment: tincture of opium versus methadone	Study population		RR 1.00 (0.95 to 1.05)	74 (1 RCT)	⊕⊕⊖⊖ LOW [2]
	1000 per 1000	1000 per 1000 (950 to 1000)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for risk of bias: high risk of selection, performance, and detection bias; unclear risk of attrition bias.
[2]Downgraded two levels for imprecision: one study with very few participants.
[3]Downgraded one level for risk of bias: high risk of performance and detection bias; unclear risk of selection bias.
[4]Downgraded one level for risk of bias: high risk of reporting bias; unclear risk of selection bias.
[5]Downgraded one level for risk of bias: high risk of performance, detection, attrition, and reporting bias; unclear risk of selection bias.
[6]Downgraded one level for risk of bias: high risk of reporting bias; unclear risk of selection and attrition bias.

Summary of findings 2. Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal

Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal

Patient or population: management of opium withdrawal
Setting: outpatient and inpatient
Intervention: pharmacological detoxification treatment
Comparison: other pharmacological detoxification treatment

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with other pharmacological detoxification treatment	Risk with pharmacological detoxification treatment			
Withdrawal symptoms at day 3: clonidine versus clonidine plus amantadine, inpatient setting	The mean withdrawal symptoms at day 3: clonidine versus clonidine plus amantadine was 9.83 days.	MD 3.56 days lower (5.97 lower to 1.15 lower)	-	60 (1 CCT)	⊕⊖⊖⊖ VERY LOW [1 2]
Withdrawal symptoms at day 3: clonidine versus buprenorphine,inpatient setting	The mean withdrawal symptoms at day 3: clonidine versus buprenorphine in inpatient setting was 12.5 days.	MD 1.4 days lower (2.93 lower to 0.13 higher)	-	34 (1 CCT)	⊕⊖⊖⊖ VERY LOW [2 3]
Withdrawal symptoms at day 3: methadone versus tramadol	The mean withdrawal symptoms at day 3: methadone versus tramadol was 8.5 days.	MD 0.04 days higher (2.68 lower to 2.76 higher)	-	72 (1 CCT)	⊕⊖⊖⊖ VERY LOW [2 4]
Withdrawal symptoms at day 3: methadone versus methadone plus gabapentin	The mean withdrawal symptoms at day 3: methadone versus methadone plus gabapentin was 13.4 days.	MD 2.2 days lower (6.72 lower to 2.32 higher)	-	40 (1 RCT)	⊕⊕⊖⊖ LOW [2]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for risk of bias: high risk of performance and detection bias; unclear risk of selection bias.
[2]Downgraded two levels for imprecision: one study with very few participants.
[3]Downgraded one level for risk of bias: high risk of reporting bias; unclear risk of selection bias.
[4]Downgraded one level for risk of bias: high risk of reporting bias; unclear risk of selection and attrition bias.

BACKGROUND

Description of the condition

Opioid dependence is a major health and social issue in most societies, but access and cultural attitudes affect the patterns of opioid use among different countries. Opium is used for pleasure, as a painkiller, a hypnotic, and for the treatment of premature ejaculation (Ahmadi 2004). In opium-cultivating countries and some of their neighbours, opium use is more common than use of other opioids. This is particularly true in Afghanistan, Laos, Myanmar, and Iran (UNODC 2011). Opium has traditionally been used in Pakistan, India, China, Thailand, Bangladesh, Nepal, Sri Lanka, Turkey, Iraq, Jordan, Egypt, Bahrain, Oman, and Kuwait, as well (Ray 2006; WHO/EMRO 2004). In some of these countries, such as in Iran, opium has always been the most widely abused illicit drug. A national survey on epidemiology of drug use in Iran showed that among the adult male population, 8.9% and 3% were current opium users and opium dependents, respectively (Iranian MoH 2002). A new national household survey from Iran also showed that opium is the main substance that leads to substance use disorders (Amin-Esmaeili 2016). A systematic review on drug use in Iranian universities reported that the prevalence of opium use ranged from 7.1% to 10.2%, and that the daily use ranged from 3.4% to 8.8% among male students. The rates were much lower in female students (Rahimi-Movaghar 2006). Another new systematic review reported opium abuse to be 4% in college and high school students (Menati 2016). A drug use survey in Afghanistan in 2005 reported the existence of about 150,000 regular opium users (0.6% of the total population) in that country (Afghanistan Counter Narcotics & UNODC 2005); in four years, this number increased to 230,000 (UNODC 2010). In India, the National Household Survey on Drug Abuse in 2002 reported that 0.5% of adult males were current (use within last month) opium users, and that there were about 1.4 million opium users in that country (Ray 2004). Another household survey in the state of Arunachal Pradesh in India showed that 6.6% of individuals aged 15 years or older were current opium users (Chaturvedi 2013). In many countries, the pattern of drug use has shifted from softer opioids to harder ones like heroin in the last decade; however, there are at least 5 million regular opium users in the world.

Opium is obtained from the unripe seed capsules of the poppy plant, *Papaver somniferum*. The milky juice is dried and powdered to make powdered opium, which contains a number of alkaloids. These alkaloids can be divided into two distinct chemical classes, phenanthrenes and benzylisoquinolines. The principal phenanthrenes are morphine (10% of opium), codeine (0.5%), and thebaine (0.2%). The principal benzylisoquinolines are papaverine (1%) and noscapine (6%) (Brunton 2006).

Opium has the properties of opioid analgesics. Its analgesic and sedative actions are due mainly to its content of morphine. However, opium acts less rapidly than morphine, since opium appears to be more slowly absorbed. The relaxing action of the papaverine and noscapine on intestinal muscle makes it more constipating than morphine. Alkaloids of opium have their own mechanisms of action. Papaverine has a direct relaxant effect on smooth muscle and causes gastrointestinal disturbance. Noscapine is a centrally acting cough suppressant. Codeine is also used for cough suppression (Sweetman 2007). Thebaine acts like strychnine, and may produce convulsions (PubChem 2008; Yamazoe 1981).

Diamorphine hydrochloride (heroin) is an acetylated morphine derivative and is a more potent opioid analgesic than morphine. Diamorphine is much more lipid-soluble and has a more rapid onset and shorter duration of action than morphine. Although deacetylation to morphine occurs rapidly in the blood, it occurs only slowly in the cerebral spinal fluid following intraspinal injection of diamorphine (Sweetman 2007).

Currently, opium continues to be consumed by traditional means, that is eating and smoking. Although in most cases opium is used occasionally and mainly in male gatherings, regular use of opium occurs and causes dependence (Ray 2006). Opium dependence is less debilitating than heroin dependence. Opium users have a more stable lifestyle than heroin users. A high proportion of opium users are married and live with their families (Jafari 2010; Razaghi 1999). Psychiatric comorbidity is significantly less in opium users than in heroin users (Ghaffarnejad 2009). Opium dependence is not a benign disorder; however, in comparison to heroin, opium costs less, requires fewer doses per day, and has a less toxic withdrawal (Westermeyer 1977).

Cessation of opium use in an individual who is opium dependent gives rise to a classical opiate withdrawal syndrome of mild intensity. The signs and symptoms of the syndrome include irritability, anxiety, apprehension, muscular and abdominal pains, chills, nausea, diarrhoea, yawning, lacrimation, sweating, sneezing, rhinorrhoea, general weakness, and insomnia. The acute physical signs of withdrawal syndrome usually stop after 14 days, but, as happens for heroin dependence, protracted syndrome that includes reduced well-being, malaise, and periodic strong cravings may continue for months. Completion of withdrawal and remaining abstinent is difficult for most opium dependents. Although relapse rate after completion of withdrawal is high, withdrawal remains a required first step for many forms of longer-term treatment (World Health Organization 2009). As opium is a less abusive and less harmful substance than heroin, and individuals with opium dependence generally have a higher socioeconomic status and less degree of psychopathology, in practice many of those with opium dependence are provided withdrawal management when referred for treatment.

Description of the intervention

Limited information is currently available on the management of opium withdrawal. Several pharmacological modalities of detoxification including alpha2 adrenergic agonists, buprenorphine, reducing dose of methadone, opioid antagonists (with minimal sedation or under heavy sedation), and symptomatic medication, with or without psychosocial treatment, have been used for opiate dependence, most of them focused on heroin users (Amato 2013; Gowing 2009a; Gowing 2009b; Gowing 2010; Gowing 2014).

Why it is important to do this review

There are no clear guidelines on how to treat individuals dependent on opium (Zarghami 2008). All guidelines for management of opioid dependence are based on evidence for managing heroin-dependent patients, which constitute the main population of opioid dependents in Western countries. However, people dependent on opium appear to differ in several ways from those who use heroin. Opium has different pharmacokinetics, adverse effects, and severity of withdrawal. In addition, modes

of administration of opium and socio-demographic characteristics of users are also different from heroin. Consequently, managing opium dependence based on evidence on management of heroin dependence is the subject of debate.

OBJECTIVES

To assess the effectiveness and safety of various pharmacological therapies for the management of the acute phase of opium withdrawal.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials and controlled clinical trials on pharmacological detoxification treatments to manage acute withdrawal from opium. The trials should have provided detailed information on the type and dose of pharmacological therapies, and have listed at least one major outcome measure.

Types of participants

Opium-dependent individuals who underwent acute withdrawal management.

Trials including participants with additional physical or psychological illness were also eligible, and there was no restriction on setting.

Types of interventions

Experimental intervention

Pharmacological detoxification treatments, including alpha2 adrenergic agonists, buprenorphine taper, methadone taper, opioid antagonists with minimal sedation, opioid antagonists under heavy sedation, taper of tincture of opium, and other pharmacologic treatments.

Control or comparison interventions

- Placebo
- No intervention
- Other pharmacological interventions alone or in combination with any psychosocial intervention
- Different dosages of the same drug for management of acute opium withdrawal
- Any psychosocial intervention

We excluded studies comparing the same pharmacologic treatment administered in different settings. We also excluded studies comparing different protocols for anaesthesia in ultrarapid opioid detoxification.

Types of outcome measures

Primary outcomes

1. Completion of treatment, as number of participants completing the detoxification programme
2. Use of opium at the end of the detoxification programme, as number of participants with positive urinalysis or number of participants having gone through naloxone challenge test or who have started naltrexone
3. Duration and severity of signs and symptoms of withdrawal, including patient self rating
4. Nature, incidence, and course of adverse effects
5. Mortality rate

We differentiated withdrawal signs and symptoms from adverse effects of treatment exactly as defined in each included study.

When the mean of withdrawal symptoms was provided for several days, we presented all results in the analysis section, and mainly focused on day 3 in the text. The reason for this is that opium withdrawal is most severe in the second to fourth day.

Secondary outcomes

1. Client satisfaction
2. Use of other abusive substances
3. Fatal or non-fatal overdose rate
4. Relapse rate at follow-up

Search methods for identification of studies

We undertook both electronic and manual searches to identify eligible studies. There was no language restriction.

Electronic searches

We searched the following international bibliographic databases:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library;
- MEDLINE via Ovid (1966 to 13 September 2017);
- Embase via Embase.com (1974 to 13 September 2017);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) via EBSCOhost (1982 to 11 September 2017);
- PsycINFO via Ovid (1887 to 11 September 2017).

We also searched the following regional and national bibliographic databases:

- IMEMR (Index Medicus for WHO Eastern Mediterranean) (1984 to 13 September 2017);
- Iranmedex (up to 13 September 2017);
- IranPsych (up to 17 March 2012; the database has not been updated since March 2012).

We searched the following trials registries:

- ClinicalTrials.gov (clinicaltrials.gov) (searched 13 September 2017);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (searched 13 September 2017);
- CenterWatch Clinical Trials Listing Service (www.centerwatch.com) (searched 22 September 2017);
- ISRCTN registry (www.isrctn.com) (searched 13 September 2017).

Searching other resources

We also searched conference proceedings likely to contain trials relevant to the review and the reference lists of all relevant papers to identify further studies.

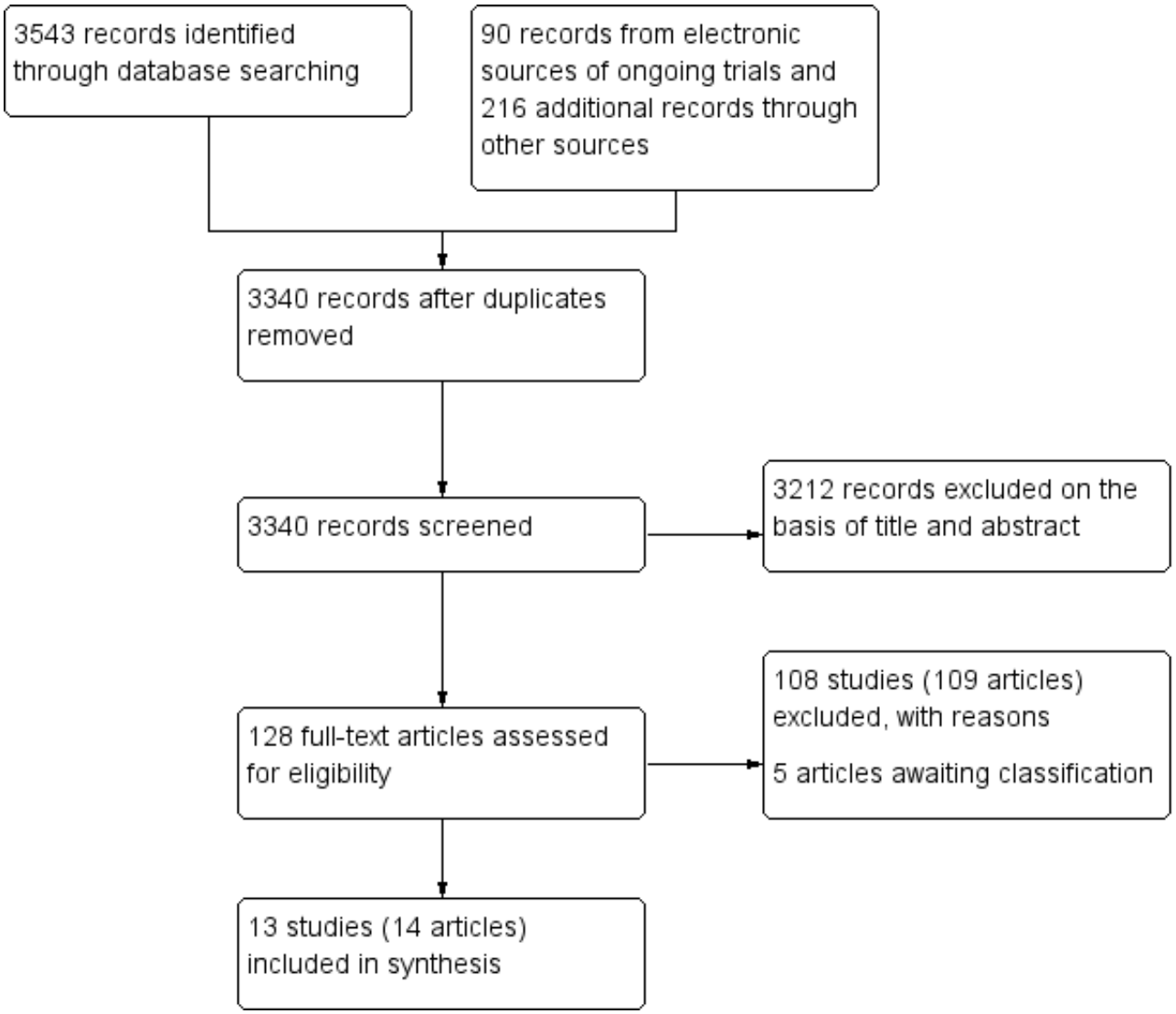
We contacted the authors of retrieved studies for missing data or incomplete trials. The full search strategies for all databases, as well as the numbers of retrieved records, are included in Appendix 1.

Data collection and analysis

Selection of studies

Two review authors (MAE, JG) inspected the reports identified by the search by reading titles and abstracts. Any disagreements were resolved through discussion with third review author (ARM). We obtained the full texts of those studies deemed potentially relevant, and two review authors (ARM, JG) assessed these for inclusion in the review. Any disagreements were resolved by discussion. The process of study selection, including the numbers of retrieved and selected documents, is presented in the flowchart according to a modified PRISMA statement (Figure 1).

Figure 1. Study flow diagram.



Data extraction and management

Two review authors (MAE, JG) independently extracted data using a data extraction form. Any disagreements were resolved through discussion with a third review author (ARM). As the included studies assessed different comparisons, we did not perform meta-analysis and summarised the key findings narratively.

We intended to extract the following data if provided in each included study.

- Study characteristics:
  - Author and year of publication
  - City and country
  - Study implementation year
  - Funding
- Methods:
  - Study design
  - Setting and sites
  - Number of arms (groups)
  - Sequence generation
  - Allocation concealment
  - Blinding of participants/therapists/assessors
  - Comparability of participants in all arms
  - Intention-to-treat analysis
  - Instruments administered to assess study outcomes
  - The person who assessed study outcomes
- Participants:
  - Eligibility criteria
  - Number of participants in each arm at baseline
  - Sex
  - Age (range, mean and standard deviation)
  - Comorbidities
  - Other drugs used
- Interventions:
  - Main pharmacologic interventions in each arm
  - Details of pharmacologic interventions (dose, frequency, duration)
  - Other interventions
  - Adherence
- Outcomes:
  - Number who completed treatment
  - Negative urinalysis for morphine at the end of detoxification programme
  - Severity of withdrawal (mean withdrawal score or number of participants who complained of each withdrawal symptom) in different days of detoxification process
  - Severity of craving (mean craving score)
  - Drug adverse effects
  - Client satisfaction
  - Use of other abusive substances
  - Mortality rate
  - Fatal and non-fatal overdose rate
  - Negative urinalysis for morphine in follow-up

Assessment of risk of bias in included studies

Two review authors (JG, ARM) independently assessed the risk of bias of the included studies using the criteria recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion The recommended approach for assessing risk of bias in studies included in a Cochrane Review is a two-part tool, addressing seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias), and other sources of bias. The first part of the tool involves describing what was reported to have occurred in the study. The second part of the tool involves assigning a judgement relating to the risk of bias for that entry, in terms of low, high or unclear risk. We used the criteria indicated by the *Cochrane Handbook for Systematic Reviews of Interventions* adapted to the addiction field to make these judgements. See Appendix 2 for details.

The domains of sequence generation and allocation concealment (avoidance of selection bias) were addressed in the tool by a single entry for each study.

We considered blinding of participants, personnel, and outcome assessment (avoidance of performance bias and detection bias) separately for objective outcomes (e.g. dropout) and subjective outcomes (e.g. duration and severity of signs and symptoms of withdrawal, adverse effects).

We considered incomplete outcome data (avoidance of attrition bias) for all outcomes except for drop out from treatment, which is frequently the primary outcome measure in trials on addiction.

Measures of treatment effect

We presented dichotomous outcomes (e.g. number of participants who completed treatment) as risk ratios (RR). We presented continuous outcomes (e.g. severity of withdrawal) as mean differences (MD). We expressed uncertainties in the results with 95% confidence intervals (CI).

When the mean of withdrawal symptoms was provided for several days, we presented all results in the analysis section, and mainly focused on day 3 in the text. The reason for this is that withdrawal from opium is most severe in the second to fourth day.

Data synthesis

Where possible, we had planned to combine the outcomes from the individual trials through meta-analysis (comparability of intervention and outcomes between trials) using a random-effects model, as we expected a certain degree of heterogeneity among trials. However, meta-analysis was not possible due to substantial differences between interventions in the studies. We reported results of the included studies individually for each trial, re-expressed as RR for dichotomous outcomes and MD for continuous outcomes with 95% CI. We presented the results using Review Manager 5 (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We would have assessed statistical heterogeneity using the I^2 statistic and the Chi^2 test (x2) (Higgins 2011). In addition, we intended to consider factors such as setting and duration of treatment as confounders, taking these into account in the analysis wherever possible. However, we did not perform sensitivity analysis due to heterogeneity among interventions and comparisons.

'Summary of findings' table

We assessed the overall quality of the evidence for the primary outcome using the GRADE system (GRADE 2004; Guyatt 2008; Guyatt 2011; Schünemann 2006), which takes into account issues not only related to internal validity but also to external validity, such as

directness of results. The 'Summary of findings' tables present the main findings of a review in a transparent and simple tabular format. In particular, they provide key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Grading is decreased for the following reasons.

- Serious (-1) or very serious (-2) study limitation for risk of bias.
- Serious (-1) or very serious (-2) inconsistency between study results.
- Some (-1) or major (-2) uncertainty about directness (the correspondence between the population, the intervention, or the outcomes measured in the studies actually found and those under consideration in our systematic review).
- Serious (-1) or very serious (-2) imprecision of the pooled estimate.
- Strong suspicion of publication bias (-1).

RESULTS

Description of studies

Results of the search

The search identified 1624 records through international bibliographic databases, 1919 through regional and national bibliographic databases, 90 through electronic sources of ongoing trials, and 216 through other sources. Five hundred and nine out of 1624 studies identified from the international databases were duplicates and were removed. In total, we screened 3340 records and excluded 3212 after our review of titles and abstracts for inclusion criteria. From the remaining 128 records, we excluded 108 studies (109 articles) after our review of the full texts. Another five studies are awaiting classification due to unavailability of the full text or inability to contact authors to inquire about the types of opioids used by participants. Finally, 13 clinical trials (from 14 articles) were considered to be eligible for the review and were included. The flow diagram of steps of the searches and the results is presented in Figure 1.

Included studies

The 13 included studies involved 1096 participants. Only two studies were randomised controlled trials (Kheirabadi 2008; Tabassomi 2016); the other studies were evaluated as controlled clinical trials. See Characteristics of included studies.

Interventions

The included studies considered 12 different comparisons.

1. Baclofen versus clonidine (1 study, 66 participants) (Ahmadi Abhari 2003).
2. Clonidine versus clonidine plus amantadine (1 study, 69 participants) (Amiri 2014).
3. Clonidine versus buprenorphine (2 studies, 111 participants) (Salehi 2007a; Ziaaddini 2012).
4. High-dose clonidine versus low-dose clonidine versus symptomatic management (1 study, 102 participants) (Satija 1988).
5. Clonidine versus methadone (1 study, 361 participants) (Taraghi 2005).
6. Methadone versus tramadol (1 study reported in 2 papers, 72 participants) (Salehi 2007b).
7. Methadone versus methadone plus gabapentin (1 study, 40 participants) (Kheirabadi 2008).
8. Gradual reduction of methadone versus sudden withdrawal (1 study, 20 participants) (Lal 1976).
9. Methadone plus amitriptyline versus methadone (1 study, 44 participants) (Salehi 2005).
10. Diphenoxylate versus propoxyphene (1 study, 105 participants) (Singh 1984).
11. Three different protocols of tincture of opium (1 study, 32 participants) (Somogyi 2008).
12. Tincture of opium versus methadone (1 study, 74 participants) (Tabassomi 2016).

Clonidine and methadone were used in six trials, and buprenorphine and tincture of opium in two trials. Maximum doses of clonidine were 0.2 to 1.2 mg/day, and maximum doses of methadone were 10 to 65 mg/day. Baclofen, tramadol, amitriptyline, gabapentin, diphenoxylate, and propoxyphene were used in one trial each. Three studies assessed different dosage or tapering mechanism for a medication, namely for clonidine, methadone, and tincture of opium.

One study had three arms (Satija 1988), comparing high-dose clonidine versus low-dose clonidine versus symptomatic treatment; we analysed the comparison between the first two arms. Another study claimed to have four arms (Singh 1984), however it actually consisted of two trials in different time frames: diphenoxylate and propoxyphene were compared in one study in high doses and in another study in low doses. The remaining 11 studies had two arms.

In 12 studies, all participants were opium dependent. In one study with 66 participants (Ahmadi Abhari 2003), 90% were opium dependent; however, separate data for the opium dependents were not available. We decided to include the study and use the data for the all 66 participants.

For a more detailed description of studies, see Characteristics of included studies.

Participants

The studies included 1096 participants, of whom only 14 (from 4 studies) were female. One study did not report the gender of the participants (Taraghi 2005). Age range was from 18 to 70 years. One

study only reported that participants were required to be under 40 (Salehi 2007a). The mean age of the total samples ranged from 25.5, in Ziaaddini 2012, to 41, in Lal 1976. Five studies provided the average amount of daily opium use in participants, which ranged from 4.8, in Singh 1984 and Taraghi 2005, to 78, in Somogyi 2008. One study required that participants use less than 2 g of opium per day (Salehi 2007a).

Settings and duration of trials

Six and five trials used outpatient and inpatient settings, respectively. Two studies did not report the setting used. The duration of detoxification programmes was 3 to 15 days in inpatient settings and 3 to 25 days in outpatient settings. The 13 studies were carried out in three countries: Iran (nine studies), India (three studies), and Thailand (one study). Six studies did not report the enrolment dates. The other studies reported enrolment dates from 1980 to 2013. Ten studies were published after 2002, and three other studies (from India) were published before 1989.

Outcomes

The included studies reported the following outcomes.

1. Number of participants completing treatment (8 studies).
2. Withdrawal scores (13 studies), using a variety of scales. The total mean withdrawal scores were provided in six studies.
3. Adverse effects (8 studies).
4. Mortality rate (3 studies).

The included studies used the following measures for assessing withdrawal signs and symptoms.

1. Short Opioid Withdrawal Scale, 10-item, subjective measure (Ahmadi Abhari 2003; Salehi 2005).
2. Clinical Opioid Withdrawal Scale (COWS), 11 symptoms, include both subjective and objective measures (Amiri 2014; Ziaaddini 2012).
3. Subjective Opiate Withdrawal Scale, 16-item (Kheirabadi 2008; Salehi 2007b).
4. Methadone Symptoms Checklist, 16-item, subjective measure (Somogyi 2008).
5. Withdrawal Symptoms Rating Scale, 24-item, objective measure (Satija 1988).
6. Adjective Rating Withdrawal Scale (ARWS), 16-item, subjective measure (Ziaaddini 2012).
7. Mental symptoms checklist, 5-item, subjective measure (Ahmadi Abhari 2003; Salehi 2005; Salehi 2007b).
8. Objective Opioid Withdrawal Scale (OOWS), 13-item, objective measure (Tabassomi 2016).

Types of comparisons

We grouped the studies into two main comparisons.

1. Pharmacological detoxification treatments versus other pharmacological detoxification interventions.
2. Pharmacological detoxification treatments versus different dosages of the same drug.

Within the two comparisons, we compared each type of pharmacological intervention.

Excluded studies

We excluded a total of 108 studies (from 109 articles). Some studies had more than one reason for exclusion. Reasons for exclusion were as follows.

- Participants not dependent on opium (85 studies).
- Types of opioids were not reported (3 studies).
- Not a controlled trial (18 studies).
- Anaesthesia procedures (5 studies).
- Not on the management of withdrawal symptoms within the first 30 days after stoppage of opium use (5 studies).
- Same pharmacologic interventions were provided in all arms (3 studies).
- No results on outcome measures provided (1 study).
- Participants were not dependent on opioids (1 study).
- Opium users were included, however despite contacting the authors, we were unable to obtain separate data for opium users (6 studies).

Risk of bias in included studies

See Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

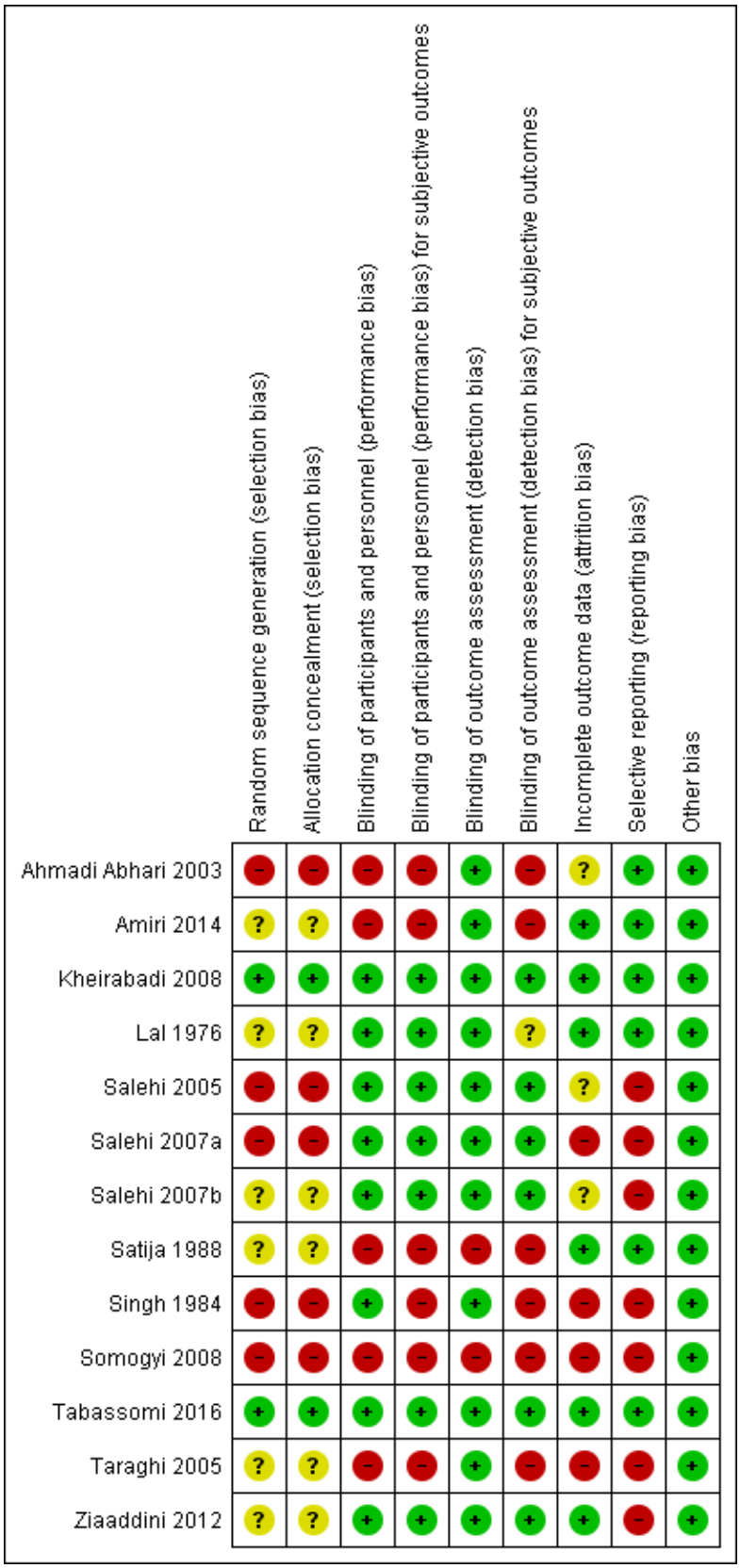
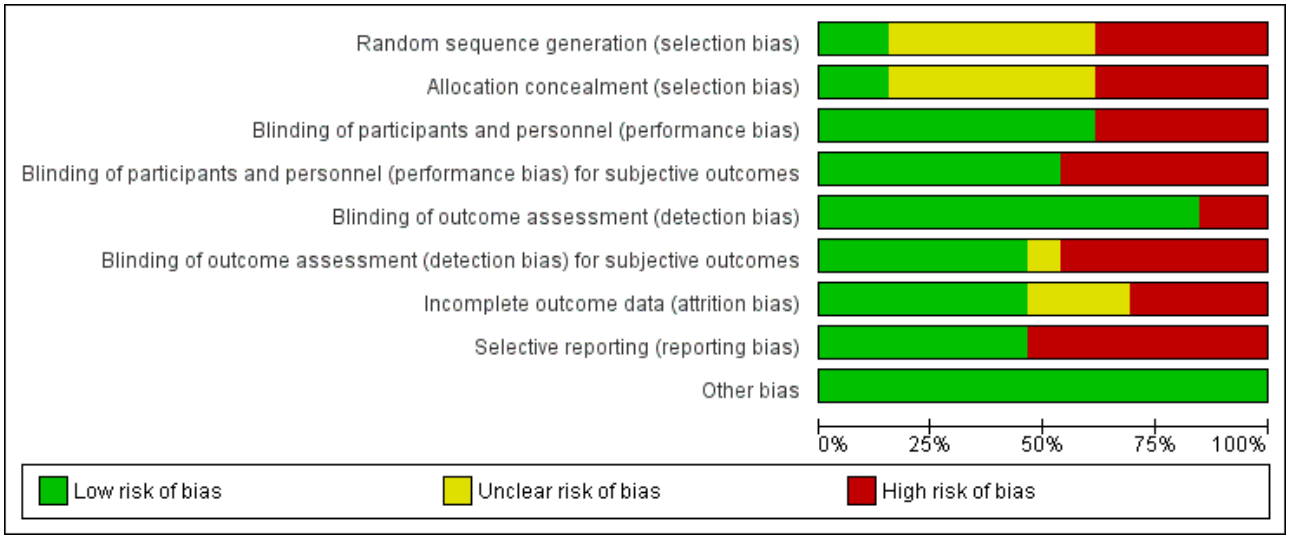


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

Of the 13 included studies, only two reported a random sequence generation method and were considered as at low risk of bias (Kheirabadi 2008; Tabassomi 2016). We judged six studies as being at unclear risk of bias because they did not provide sufficient information about method of sequence generation (Amiri 2014; Lal 1976; Salehi 2007b; Satija 1988; Taraghi 2005; Ziaaddini 2012). We judged five studies as being at high risk of bias (Ahmadi Abhari 2003; Salehi 2005; Salehi 2007a; Singh 1984; Somogyi 2008): Ahmadi Abhari 2003 and Salehi 2007a used alternate assignment; Salehi 2005 reported assignment based on the order of presentation; and Somogyi 2008 reported allocation depending on participants' self reported prior opium use.

Allocation concealment

Of the 13 included studies, only two reported allocation concealment and were considered as at low risk of bias (Kheirabadi 2008; Tabassomi 2016). We judged six studies as being at unclear risk of bias because they did not provide sufficient information about allocation concealment method (Amiri 2014; Lal 1976; Salehi 2007b; Satija 1988; Taraghi 2005; Ziaaddini 2012). We judged five studies in which allocation concealment was not done as being at high risk of bias (Ahmadi Abhari 2003; Salehi 2005; Salehi 2007a; Singh 1984; Somogyi 2008).

Blinding

Performance bias for objective outcomes

Seven studies provided detailed information about blinding of participants and personnel and were considered as at low risk of bias for this domain (Kheirabadi 2008; Lal 1976; Salehi 2005; Salehi 2007a; Salehi 2007b; Tabassomi 2016; Ziaaddini 2012). Singh 1984 did not assess any objective outcomes. We judged the remaining five studies as at high risk of bias: four studies were not blinded (Ahmadi Abhari 2003; Amiri 2014; Somogyi 2008; Taraghi 2005), and Satija 1988 stated that the drugs were given in identical capsules and that participants and the evaluating doctor were blinded, but we judged that blinding was impossible because of symptomatic therapy in one of the study groups.

Performance bias for subjective outcomes

Seven studies provided detailed information about blinding of participants and personnel and were considered as at low risk of bias for this domain (Kheirabadi 2008; Lal 1976; Salehi 2005; Salehi 2007a; Salehi 2007b; Tabassomi 2016; Ziaaddini 2012). We judged the remaining six studies to be at high risk of bias: four studies were not blinded (Ahmadi Abhari 2003; Amiri 2014; Somogyi 2008; Taraghi 2005); Satija 1988 stated that the drugs were given in identical capsules and that participants and the evaluating doctor were blinded, but we judged that blinding was impossible because of symptomatic therapy in one of the study groups; and in Singh 1984 blinding of participants was done for the type of medication but not for the dose of medications.

Detection bias for objective outcomes

Six studies provided detailed information about blinding of outcome assessors and were considered as being at low risk of bias for this domain (Kheirabadi 2008; Salehi 2005; Salehi 2007a; Salehi 2007b; Tabassomi 2016; Ziaaddini 2012). Singh 1984 did not assess any objective outcomes. In four studies, either blinding of outcome assessment was not done (Ahmadi Abhari 2003; Amiri 2014; Taraghi 2005), or the provided information was insufficient (Lal 1976); however, for assessment of the main objective outcome (completion of treatment), it is unlikely that the assessment was affected by lack of blinding of the assessors. In the two remaining studies (Satija 1988; Somogyi 2008), blinding of outcome assessment was not done, and vital signs were assessed as objective outcomes, therefore we considered these two studies to be at high risk of detection bias.

Detection bias for subjective outcomes

Six studies provided detailed information about blinding of outcome assessors and were considered as being at low risk of bias for this domain (Kheirabadi 2008; Salehi 2005; Salehi 2007a; Salehi 2007b; Tabassomi 2016; Ziaaddini 2012). We judged Lal 1976

as at unclear risk of bias because they did not provide sufficient information on blinding of outcome assessment. In six studies blinding of outcome assessors was not done (Ahmadi Abhari 2003; Amiri 2014; Satija 1988; Singh 1984; Somogyi 2008; Taraghi 2005), therefore assessment of subjective outcomes, such as subjective withdrawal symptoms and adverse effects, was prone to high risk of bias.

Incomplete outcome data

We considered incomplete outcome data for all outcomes except completion of treatment (or dropout). Of the 13 studies, we judged six as being at low risk of attrition bias (Amiri 2014; Kheirabadi 2008; Lal 1976; Satija 1988; Tabassomi 2016; Ziaaddini 2012). In Amiri 2014, the two study groups were reported to have nearly equal non-compliance and loss to follow-up cases (i.e. 5 out of 35 (14.3%) in the clonidine group versus 4 of 34 (11.8%) in the clonidine plus amantadine group). Kheirabadi 2008 reported 3 of 20 excluded participants (15%) in the placebo group and none in the gabapentin group, which is unlikely to result in biased estimates. Lal 1976 and Tabassomi 2016 had no missing data. Satija 1988 reported that an equal number of participants dropped out in the three groups (4 of 34 in each group (11.8%)); Ziaaddini 2012 reported that only 1 of 21 participants (4.8%) in the clonidine group and none of 14 participants in the buprenorphine group discontinued treatment. There was insufficient information in three studies (Ahmadi Abhari 2003; Salehi 2005; Salehi 2007b), which we considered as at unclear risk of bias. We judged the remaining four studies to be at high risk of bias (Salehi 2007a; Singh 1984; Somogyi 2008; Taraghi 2005). Salehi 2007a reported 13 dropouts from a total of 89 participants (14.6%), of which 4 were due to hypotension (group not reported), and 7 in the clonidine group versus 2 in the buprenorphine group were due to losses to follow-up and may have induced bias in effect estimates. Singh 1984 reported 15 dropouts of 105 participants (14.3%), and Somogyi 2008 reported 13 dropouts of 45 participants (28.9%), but their groups were not reported. Taraghi 2005 reported 20 dropouts of 120 participants (16.7%) in the clonidine group and 141 dropouts of 241 participants (58.5%) in the methadone group, but some key outcomes like adverse effects were reported only in those who completed treatment.

Selective reporting

In eight studies (Ahmadi Abhari 2003; Amiri 2014; Kheirabadi 2008; Lal 1976; Salehi 2007b; Satija 1988; Tabassomi 2016; Taraghi 2005), the outcomes presented in the results section were consistent with those specified in the methods section. Amiri 2014 was registered in the Iranian Clinical Trials Registry, and the presented outcomes were consistent with the registered protocol. We considered five studies as being at high risk of reporting bias (Salehi 2005; Salehi 2007a; Singh 1984; Somogyi 2008; Ziaaddini 2012). Salehi 2005 did not report completion rate of treatment in the 25 days, and mean of total withdrawal score at days 7, 15, 17, and 25. Salehi 2007a, Singh 1984, and Somogyi 2008 did not report completion rate. In Ziaaddini 2012, the rate of positive urinary samples for opioids at the end of six months was reported as one of the main outcomes of the study, but the results are not presented, and there is no report about side effects.

In addition, there were reporting errors in two studies (Salehi 2007b; Taraghi 2005). In Salehi 2007b, the difference between the two groups in mean mental score at day 15 is reported as significant, but as obtained from the results tables it is insignificant. There are several reporting errors in Taraghi 2005: for example, the rates presented for patient satisfaction in each group are not matched with the reported significance of difference (P value).

Six studies did not report source of funding. In the remaining studies, academic institutions were mainly reported as the source of funding. Only one study mentioned funding from a pharmaceutical company (Singh 1984), for which two companies had provided the two compared medications.

Effects of interventions

See: **Summary of findings for the main comparison** Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal; **Summary of findings 2** Pharmacological detoxification treatment compared to other pharmacological detoxification treatment for management of opium withdrawal

As the included trials investigated outcomes of different comparisons, it was not possible to perform meta-analysis.

Primary outcomes

Comparison 1: Pharmacological detoxification treatments versus other pharmacological detoxification interventions

1.1 Completion of treatment

See Summary of findings for the main comparison.

1.1.1 Baclofen versus clonidine

One study involving 66 participants found no difference between groups (risk ratio (RR) 1.06, 95% confidence interval (CI) 0.63 to 1.80; very low-quality evidence) (Ahmadi Abhari 2003).

1.1.2 Clonidine versus clonidine plus amantadine

One study involving 69 participants found no difference between groups (RR 1.03, 95% CI 0.86 to 1.24; very low-quality evidence) (Amiri 2014).

1.1.3 Clonidine versus buprenorphine in an inpatient setting

One study involving 35 participants found no difference between groups (RR 1.04, 95% CI 0.90 to 1.20; very low-quality evidence) (Ziaaddini 2012).

1.1.4 Clonidine versus methadone

One study involving 361 participants found that people taking clonidine were twice as likely to complete treatment as those taking methadone (RR 2.01, 95% CI 1.69 to 2.38; low-quality evidence) (Taraghi 2005).

1.1.5 Methadone versus tramadol

One study involving 72 participants found no difference between groups (RR 0.95, 95% CI 0.65 to 1.37; very low-quality evidence) (Salehi 2007b).

1.1.6 Methadone versus methadone plus gabapentin

One study involving 40 participants found no difference between groups (RR 1.17, 95% CI 0.96 to 1.43; low-quality evidence) (Kheirabadi 2008).

1.1.7 Tincture of opium versus methadone

One study involving 74 participants found that all participants completed treatment in both groups (RR 1.00, 95% CI 0.95 to 1.05; low-quality evidence) (Tabassomi 2016).

For all see Analysis 1.1.

1.2 Duration and severity of signs and symptoms of withdrawal at day 3 of treatment

See Summary of findings 2.

1.2.1 Clonidine versus clonidine plus amantadine

One study involving 60 participants found that adding amantadine to clonidine decreased withdrawal scores rated at day 3 (mean difference (MD) -3.56, 95% CI -5.97 to -1.15; very low-quality evidence) (Amiri 2014).

1.2.2 Clonidine versus buprenorphine in an inpatient setting

One study involving 34 participants found no difference between groups using the Clinical Opiate Withdrawal Scale at day 3, rated by a psychiatrist (MD -1.40, 95% CI -2.93 to 0.13). Furthermore, this study found results in favour of buprenorphine using the Adjective Rating Withdrawal Scale at day 3, rated by participants (MD -11.80, 95% CI -15.56 to -8.04; very low-quality evidence) (Ziaaddini 2012).

1.2.3. Clonidine versus buprenorphine in an outpatient setting

One study involving 76 participants found that a smaller number of participants experienced severe withdrawal symptoms in the buprenorphine group at day 3 (RR 0.35, 95% 0.19 to 0.64; very low-quality evidence) (Salehi 2007a).

1.2.4 Methadone versus tramadol

One study involving 72 participants found no difference between groups using mean withdrawal score at day 3 (MD 0.04, 95% CI -2.68 to 2.76). In addition, the difference in mean mental withdrawal score at day 3 did not differ between groups (MD -0.23, 95% CI -2.10 to 1.64; very low-quality evidence) (Salehi 2007b).

1.2.5 Methadone versus methadone plus gabapentin

One study involving 40 participants found no difference between groups at day 3 (MD -2.20, 95% CI -6.72 to 2.32; low-quality evidence) (Kheirabadi 2008).

For all see Analysis 1.2.

Comparing baclofen versus clonidine, one study involving 66 participants found no difference between groups at days 0, 1, 2, 3, 4, 7, and 14 (results provided only by graphs) (Ahmadi Abhari 2003).

Comparing clonidine versus methadone, one study involving 361 participants assessed the severity of 10 withdrawal symptoms and found that dysphoria, agitation, irritability, muscle aches, yawning, and hot flashes were more severe in the clonidine group (Taraghi 2005). However, the time and number of assessments were not reported.

Comparing methadone plus amitriptyline versus methadone, one study involving 44 opium participants found no difference between groups in mean withdrawal score; lower mental withdrawal scores at days 7 and 25 in the amitriptyline group, but not at days 15 and 17; and lower scores on the McGill Pain Questionnaire at days 15, 17, and 25 in the amitriptyline group, but not at day 7 (Salehi 2005).

One study with 105 participants involved four groups: low-dose diphenoxylate, low-dose propoxyphene, high-dose diphenoxylate, and high-dose propoxyphene (Singh 1984). Comparing low doses of diphenoxylate and propoxyphene, insomnia and diarrhoea were significantly lower in the diphenoxylate group. The study found no differences between these groups with regard to other withdrawal symptoms. Comparing high doses of diphenoxylate and propoxyphene, the study found no difference in the number of participants with each of eight withdrawal symptoms. Although there was no randomisation process between low and high dose of each medication, the authors concluded that symptoms were lower in the high-dose regimen than in the low-dose regimen.

Use of opium at the end of detoxification programme: number of participants with positive urinalysis, or number of participants to have gone through naloxone challenge test or to have started naltrexone

Only one study involving 35 participants, comparing clonidine versus buprenorphine in an inpatient setting, reported data on participants staying in naltrexone treatment at 6 months, showing no difference between groups (RR 1.50, 95% CI 0.80 to 2.82) (Ziaaddini 2012).

Adverse effects

Comparing baclofen versus clonidine, one study involving 66 participants assessed severity of adverse effects at days 0, 1, 2, 3, 4, 7, and 14, and showed no difference between groups (only graphs were provided) (Ahmadi Abhari 2003). Only two adverse effects, euphoria (46.7% in the baclofen group versus 0% in the clonidine group, $P < 0.01$) and vomiting (33% in the baclofen group versus 0% in the clonidine group, $P < 0.05$) were significantly more frequent in the baclofen group.

Comparing clonidine versus buprenorphine in an outpatient setting, one study involving 76 participants reported that 4 participants dropped out due to hypotension, but it is not specified to which group they were allocated, and these four cases have been removed from analysis (Salehi 2007a). In the 76 participants that remained in treatment, hypotension, headache, sedation, dizziness, dry mouth, nausea, constipation, and sweating were assessed and reported every day from day 1 to day 10. More adverse effects were reported in the clonidine group. Significantly higher numbers of participants in the clonidine group experienced hypotension at days 5 to 8, headache at days 1 to 8, sedation at days 5 to 8, dizziness and dry mouth at days 1 to 10, and nausea at days 1 to 9. Sweating was reported in a significantly higher number of participants in the buprenorphine group at days 1 to 10.

Comparing clonidine versus buprenorphine in an inpatient setting, one study involving 35 participants did not report adverse effects (Ziaaddini 2012), stating only that one participant in the clonidine group left the study before completion, on the second day due to blood pressure below 90/60 mmHg.

Comparing methadone versus tramadol, one study involving 72 participants reported no difference between groups for side effect scores on day 7 (Salehi 2007b). On day 14, participants in the methadone group had significantly more drowsiness ($P = 0.0195$)

and sweating (P = 0.003) than those in tramadol group (very low-quality evidence).

Comparing tincture of opium versus methadone, one study involving 74 participants found no difference between groups in the incidence of all nine adverse effects evaluated (headache, dizziness, sleepiness, misbalance, constipation, nausea, perspiration, tension, and respiratory depression) (Tabassomi 2016).

Comparing diphenoxylate versus propoxyphene, one study involving 105 participants reported no adverse effects with low-dose regimens (Singh 1984); one participant on high-dose diphenoxylate reported constipation, and two participants on high-dose propoxyphene reported mild giddiness.

Mortality rate

No deaths were reported in the included studies.

Comparison 2: Pharmacological detoxification treatments versus different dosages of the same drug

Completion of treatment

Comparing high-dose clonidine versus low-dose clonidine, one study involving 68 participants found no difference between the two groups for completion of treatment (RR 1.00, 95% CI 0.84 to 1.19) (Satija 1988).

Comparing gradual reduction of methadone versus sudden withdrawal of methadone, one study involving 20 participants reported that all participants were retained for 15 days in treatment, although completion of treatment was not reported as an outcome measure (Lal 1976).

Withdrawal symptoms

Comparing gradual reduction of methadone versus sudden withdrawal of methadone, one study involving 20 participants reported that the number of participants complaining of withdrawal symptoms during treatment was higher in the "gradual reduction" group than in the "stable dose and sudden withdrawal" group (RR 2.25, 95% CI 1.02 to 4.94) (Lal 1976). The number of participants with body aches and pain, insomnia, rhinorrhoea, diarrhoea, nervousness and tremor was higher in the "gradual reduction" group. In addition, symptoms were reported to be more severe and tended to persist throughout the period of withdrawal in the "gradual reduction" group.

Adverse effects

Comparing high-dose clonidine versus low-dose clonidine, one study involving 60 participants reported that more participants experienced hypotension in the high-dose group (RR 3.25, 95% CI 1.77 to 5.98), however no definition was provided for hypotension and no participant required specific therapy to treat hypotension (Satija 1988).

Gradual reduction of methadone was associated with more adverse effects than abrupt withdrawal of methadone (RR 2.25, 95% CI 1.02 to 4.94; 1 study, 20 participants, very low-quality evidence), (Lal 1976).

Comparing three different protocols of tincture of opium, one study involving 45 participants reported no significant adverse effects in all three groups (Somogyi 2008).

Mortality rate

No deaths were reported in the included studies.

No useful data were provided for all the other primary outcomes.

Secondary outcomes

We intended to extract and present data for our secondary outcomes as well, however only one study, 35 participants, reported results at six-month follow-up, and showed no significant difference between groups (RR 1.50, 95% CI 0.80 to 2.82; very low-quality evidence) (Ziaaddini 2012).

No other reliable data on the secondary outcomes were provided in the included studies.

DISCUSSION

Summary of main results

Regular use of opium can lead to physical and psychological dependence. Opium dependence imposes a considerable burden on societies, being associated with decreased productivity, family problems, crime, and increased healthcare costs. It is important to use specific evidence for management of opium dependence and to understand to what degree the evidence for treatment of heroin dependence applies to opium dependence as well.

In most Asian countries, detoxification is more accessible and affordable than maintenance treatment. Another review on maintenance treatment of opium was inconclusive regarding the effective maintenance management of opium dependence (Rahimi-Movaghar 2013).

We included 13 trials involving 1096 participants in this review. The 13 trials evaluated 12 different comparisons, and no pooled analysis was possible. Studies were carried out in three countries, Iran (nine studies), India (three studies), and Thailand (one study). Six studies were conducted in outpatient settings and five in inpatient settings. In two studies the setting was not described. The quality of the evidence was generally very low.

In the five studies carried out in inpatient settings, the reported completion rate ranged from 86% to 100%. In the five studies carried out in outpatient settings and assessing this outcome, completion rate ranged from 41% to 100%. No case of mortality was reported in the 13 included studies (although most studies did not mention that there were no deaths). These results show an overall promise with withdrawal management of opium.

In the single comparisons, we found low-quality evidence that clonidine was better than methadone for number of participants completing treatment. We found no difference between groups for this outcome for any of the other comparisons. Regarding withdrawal symptoms, adding amantadine to clonidine decreased withdrawal scores at days 1 to 3, and buprenorphine was superior to clonidine in controlling severe withdrawal symptoms in the first week in an outpatient setting. We found no differences for all the other comparisons.

Regarding adverse effects, more adverse effects were reported with clonidine when compared with buprenorphine in an outpatient setting, in particular a higher number of participants with hypotension was reported with high-dose clonidine.

No analysis was possible for three comparisons, since only graphs or P values were provided in the papers. These comparisons were diphenoxylate versus propoxyphene, three different protocols of opium tincture, and the addition of amitriptyline to methadone.

Overall completeness and applicability of evidence

We intended to answer the question regarding the most effective interventions for management of opium withdrawal. However, based on this review we were unable to answer this question. This review presented 12 different comparisons, the evidence for which was generally of very low quality. The included studies were carried out mainly in Iran, with a few in India and Thailand. Four of the 13 included studies were published in the Persian language. Specifically, Iran is a country with a high rate of opium use and a high number of publications on opioids (Rahimi-Movaghar 2015). The included studies suffer for low internal validity. In terms of external validity, it should be noted that the included studies involved 1096 participants, who were from the part of the world with the highest prevalence of opium use and dependence. However, women were underepresented in the study population, and an inpatient setting was used in many of the studies, which in the actual world is not the case, as most opium dependents go through detoxification in outpatient settings. All studies assessed severity of withdrawal symptoms during treatment, but with different scales. Other main outcomes such as completion of treatment and adverse effects were not assessed in all studies. Other objective outcomes, such as urinalysis for morphine and naloxone challenge test at the end of detoxification, were rarely investigated.

Quality of the evidence

Our GRADE assessment of the quality of the evidence of the included studies was very low. The major flaws in the studies were risk of selection, performance, detection, attrition, and reporting bias. In addition, sample size was very small in all of the included studies, therefore the results were highly imprecise.

Potential biases in the review process

We contacted study authors to request unpublished data and were able to obtain significant data for this review.

Agreements and disagreements with other studies or reviews

Two previous systematic reviews assessed similar comparisons in opioid-dependent individuals:

1. Gowing 2009a compared buprenorphine with clonidine for management of opioid withdrawal (10 studies) and found that buprenorphine was superior than clonidine in controlling withdrawal symptoms, which was similar to our findings. However, we included one study with very low-quality evidence reporting no difference between groups in completion rate of opium dependents in an inpatient setting, which differed from the findings of Gowing 2009a;
2. Gowing 2014 compared methadone and clonidine for management of opioid withdrawal (9 studies, 659 participants) and found no difference between groups in completion rate. However, we found low-quality evidence from one study that completion rate in opium dependents was higher with clonidine than with tapering doses of methadone.

AUTHORS' CONCLUSIONS

Implications for practice

Due to generally very low-quality evidence and small or no differences between treatments, we could make no definitive conclusions regarding the use of any specific pharmacological approach for the management of opium withdrawal. However, it seems that opium withdrawal symptoms are significant, especially at days 2 to 4 after discontinuation of opium, and patients need pharmacologic assistance for passing through the detoxification process.

The trials included in this study were carried out in a variety of inpatient and outpatient settings. Completion of treatment in the inpatient settings was generally high. However, this benefit should be weighed with the expenses of inpatient management. Withdrawal management is safe and can be provided in outpatient settings as well. However, since withdrawal management does not equate with treatment of dependence, long-term care is necessary to prevent a return to opium use.

Implications for research

This review showed that little is known about the withdrawal management of opium with specific medications. There is a need for well-designed, well-reported studies assessing alpha2 adrenergic agonists, buprenorphine, methadone, and tincture of opium. More specifically, further studies comparing clonidine with buprenorphine might be helpful in determining the effectiveness of these medications on detoxification from opium. Since withdrawal from opium is less severe than from heroin, many patients might be effectively managed in outpatient settings with less cost. Carrying out trials in outpatient settings will therefore increase the utilisation of the results in general practice.

Most of the included studies had serious risks of biases. Future studies should apply appropriate randomisation methods with adequate allocation concealment. For all dropped-out cases, the reasons and time of dropping out, as well as the group to which each case belonged, should be provided. The number of participants who have been assessed in each arm should be provided for all measures. It is recommended that published and well-studied questionnaires or checklists be used for the assessment of withdrawal symptoms and that a total score in predetermined times for each person be calculated and the mean withdrawal score for those in each intervention arm be provided. Providing the scores in addition to graphs will increase the utility of data in future reviews. The most frequently assessed days in the studies are days 3, 5, and 7, and providing data for these days will allow comparisons of results between studies. Peak withdrawal score is also a good measure that makes it possible to compare interventions with different durations. Carrying out urine tests for opium is recommended as an appropriate outcome measure for assessing successful completion of withdrawal management. Adverse effects should also be

reported specifically for each intervention arm to allow for a safety comparison. It is also recommended that in studies in which individuals with dependence to a variety of opioids are included, the results be provided separately for each type of opioid.

ACKNOWLEDGEMENTS

We wish to thank Silvia Minozzi for her contribution on methodological issues, Mitra Hefazi and Elaheh Sahimi-Izadian for their contribution to developing the protocol of this review, and to acknowledge support from Zuzana Mitrova. We appreciate the kind co-operation of Mehrdad Eftekhar, Samaneh Farnia, Ayyob Malek, Bahman Salehi, Andrew Somogyi, and Hassan Ziaaddini and for providing information that was not reported in their papers.

REFERENCES

References to studies included in this review

Ahmadi Abhari 2003 *{published data only}*

Ahmadi Abhari SA, Shabani A, Akhundzadeh Sh, Asadi SM. Baclofen and clonidine in opioid detoxification. *Iranian Journal of Psychiatry and Clinical Psychology (Andeesheh Va Raftar)* 2003;**8**(31):26-35.

Amiri 2014 *{published and unpublished data}*

Amiri S, Malek A, Tofighnia F, Asl BH, Seidy A. Amantadine as augmentation in managing opioid withdrawal with clonidine: a randomized controlled trial. *Iranian Journal of Psychiatry* 2014;**9**(3):142-6.

Kheirabadi 2008 *{published data only}*

*Kheirabadi GR, Ranjkesh M, Maracy MR, Salehi M. Effect of add-on gabapentin on opioid withdrawal symptoms in opium-dependent patients. *Addiction* 2008;**103**(9):1495-9.

Kheirabadi GR, Ranjkesh M, Maracy MR, Salehi M. "Effect of add-on gabapentin on opioid withdrawal symptoms in opium-dependent patients": Corrigendum. *Addiction* 2009;**104**(10):1776.

Lal 1976 *{published data only}*

Lal B, Singh G. Experiences of a methadone detoxification programme for opium addicts. *Drug and Alcohol Dependence* 1976;**1**(6):391-8.

Salehi 2005 *{published and unpublished data}*

Salehi M, Mir Khalaf A, Barekatain M. Amitriptyline efficacy in control of acute opioid withdrawal syndrome. *Koomesh, Journal of Semnan University of Medical Sciences* 2005;**6**(3):195-200.

Salehi 2007a *{published and unpublished data}*

Salehi B, Jafarinia N, Ghebleh F, Mansori A. A comparative study on opium withdrawal of buprenorphine and clonidine. *Journal of Qazvin University of Medical Sciences* 2007;**11**(3):57-65.

Salehi 2007b *{published data only}*

* Salehi M, Amanatkar M, Barekatain M. Comparison of the efficacy of methadone and tramadol in opioid-assisted detoxification. *Iranian Journal of Medical Sciences* 2007;**33**(1):28-31.

Salehi M, Amanatkar M, Barekatain M. Tramadol versus methadone for the management of acute opioid withdrawal: an add-on study. *Journal of Research in Medical Sciences* 2006;**11**(3):185-9.

Satija 1988 *{published data only}*

Satija DC, Natani GD, Purohit DR, Gaur R, Bhati GS. A double blind comparative study of usefulness of clonidine and symptomatic therapy in opiate detoxication. *Indian Journal of Psychiatry* 1988;**30**(1):55-9.

Singh 1984 *{published data only}*

Singh G, Singh Sachdeva J, Kumar A. A double blind comparative study of usefulness of diphenoxylate and propoxyphene napsylate in the withdrawal treatment of opium addicts. *Indian Journal of Psychiatry* 1984;**26**(4):343-8.

Somogyi 2008 *{published and unpublished data}*

Somogyi AA, Larsen M, Abadi RM, Jittiwutikarn J, Ali R, White JM. Flexible dosing of tincture of opium in the management of opioid withdrawal: pharmacokinetics and pharmacodynamics. *British Journal of Clinical Pharmacology* 2008;**66**(5):640-7.

Tabassomi 2016 *{published data only}*

Tabassomi F, Zarghami M, Shiran MR, Farnia S, Davoodi M. Opium tincture versus methadone syrup in management of acute raw opium withdrawal: a randomized, double-blind, controlled trial. *Journal of Addictive Diseases* 2016;**35**(1):8-14.

Taraghi 2005 *{published data only}*

Taraghi Sh, Pour Afkari N, Seidi A. A comparative study of effectiveness of two methods of detoxification in opium dependent patients. *Medical Journal of Tabriz University of Medical Sciences & Health Services* 2005;**27**(3):41-6.

Ziaaddini 2012 *{published and unpublished data}*

Ziaaddini H, Nasirian M, Nakhaee N. Comparison of the efficacy of buprenorphine and clonidine in detoxification of opioid-dependents. *Addiction & Health* 2012;**4**(3-4):79-86.

References to studies excluded from this review

Akhondzadeh 2000 *{published data only}*

Akhondzadeh S, Ahmadi-Abhari SA, Assadi SM, Shabestari OL, Kashani AR, Farzanehgan ZM. Double-blind randomized controlled trial of baclofen vs clonidine in the treatment of opiates withdrawal. *Journal of Clinical Pharmacy and Therapeutics* 2000;**25**(5):347-53.

Alam 2001 *{published data only}*

Alam Ansari M, Ahmed Wagan M, Ahmed Shaikh R, Ali M. Role of clonidine in acute opioid abstinence syndrome. *Pakistan Journal of Medical Sciences* 2001;**17**(3):163-8.

Ansari 2007 *{published data only}*

Ansari MA, Ahmed SP, Ali M. Calcium channel blocker verapamil: a nonhormonal option for hot flashes management in patients with acute opioid abstinence syndrome. *Pakistan Journal of Medical Sciences* 2007;**23**(3):353-7.

Assadi 2004 *{published and unpublished data}*

Assadi SM, Hafezi M, Mokri A, Razzaghi EM, Ghaeli P. Opioid detoxification using high doses of buprenorphine in 24 hours: a randomized, double blind, controlled clinical trial. *Journal of Substance Abuse Treatment* 2004;**27**(1):75-82.

Hafezi M, Asaadi SM, Razzaghi OM, Mokri A. High dose of buprenorphine in one-day opium detoxification: clinical trial. *Iranian Journal of Psychiatry and Clinical Psychology (Andeesheh Va Raftar)* 2005;**10**(3):195-202.

Badiei 2005 *{published and unpublished data}*

Badiei MM, Eftekhar M. Rapid and clonidine detoxification in opium dependent patients. *Iranian Journal of Psychiatry and Clinical Psychology (Andeesheh Va Raftar)* 2005;**10**(3):203-13.

Bearn 1996 *{published data only}*

Bearn J, Gossop M, Strang J. Randomised double-blind comparison of lofexidine and methadone in the in-patient treatment of opiate withdrawal. *Drug and Alcohol Dependence* 1996;**43**(1-2):87-91.

Bearn 2001 *{published and unpublished data}*

Bearn J, Bennett J, Martin T, Gossop M, Strang J. The impact of naloxone/lofexidine combination treatment on the opiate withdrawal syndrome. *Addiction Biology* 2001;**6**(2):147-56.

Becker 2001 *{published data only}*

Becker AB, Strain EC, Bigelow GE, Stitzer ML, Johnson RE. Gradual dose taper following chronic buprenorphine. *American Journal on Addictions* 2001;**10**(2):111-21.

Bertschy 1997 *{published data only}*

Bertschy G, Bryois C, Bondolfi G, Velardi A, Budry P, Dascal D, et al. The association carbamazepine-mianserin in opiate withdrawal: a double blind pilot study versus clonidine. *Pharmacological Research* 1997;**35**(5):451-6.

Beswick 2003 *{published data only}*

Beswick T, Best D, Bearn J, Gossop M, Rees S, Strang J. The effectiveness of combined naloxone/lofexidine in opiate detoxification: results from a double-blind randomized and placebo-controlled trial. *American Journal on Addictions* 2003;**12**(4):295-305.

Bisaga 1997 *{published data only}*

Bisaga A, Gianelli P, Popik P. Opiate withdrawal with dextromethorphan. *American Journal of Psychiatry* 1997;**154**(4):584.

Brewer 1998 *{published data only}*

Brewer C, Laban M, Schmulian C, Gooberman L, Kasvikis Y, Maksoud NA. Rapid opiate detoxification and naltrexone induction under general anaesthesia and assisted ventilation: experiences with 510 patients in four different centres. *Acta Psychiatrica Belgica* 1998;**98**:181-9.

Bruce 1964 *{published data only}*

Bruce DW. Amiphenazole in the treatment of morphine and opium addiction. *Lancet* 1964;**1**(7341):1010-2.

Buntwal 2000 *{published data only}*

Buntwal N, Bearn J, Gossop M, Strang J. Naltrexone and lofexidine combination treatment compared with conventional lofexidine treatment for in-patient opiate detoxification. *Drug and Alcohol Dependence* 2000;**59**(2):183-8.

Carnwath 1998 *{published data only}*

Carnwath T, Hardman JA. Randomised double-blind comparison of lofexidine and clonidine in the out-patient treatment of opiate withdrawal. *Drug and Alcohol Dependence* 1998;**50**(3):251-4.

Curran 2001 *{published data only}*

Curran HV, Kleckham J, Bearn J, Strang J, Wanigaratne S. Effects of methadone on cognition, mood and craving in detoxifying opiate addicts: a dose-response study. *Psychopharmacology* 2001;**154**(2):153-60.

De Jong 2005 *{published data only}*

De Jong CAJ, Laheij RJF, Krabbe PFM. General anaesthesia does not improve outcome in opioid antagonist detoxification treatment: a randomized controlled trial. *Addiction* 2005;**100**(2):206-15.

Dunn 2015 *{published data only}*

Dunn KE, Saulsgiver KA, Miller ME, Nuzzo PA, Sigmon SC. Characterizing opioid withdrawal during double-blind buprenorphine detoxification. *Drug and Alcohol Dependence* 2015;**151**:47-55.

Eftekhar 2005 *{published data only}*

Eftekhar E, Taghva A. Rapid detoxification of opium dependent patients via opioid antagonist. *Iranian Journal of Psychiatry and Clinical Psychology (Andeesheh Va Raftar)* 2005;**10**(3):214-9.

Erlendson 2017 *{published data only}*

Erlendson MJ, D'Arcy N, Encisco EM, Yu JJ, Rincon-Cruz L, Peltz G, et al. Palonosetron and hydroxyzine pre-treatment reduces the objective signs of experimentally-induced acute opioid withdrawal in humans: a double-blinded, randomized, placebo-controlled crossover study. *American Journal of Drug and Alcohol Abuse* 2017;**43**(1):78-86.

Espinosa 2001 *{published data only}*

Espinosa Berenguel JL, Palazon Sanchez C, Felices Abad F, Garcia Basterrechea JM, Gil Rueda B, Blanco Molina TB, et al. Study of an ultrashort opiate detoxification protocol in an intensive care unit: preliminary results. *Medicina Intensiva* 2001;**25**(6):217-22.

Favrat 2006 *{published and unpublished data}*

Favrat B, Zimmermann G, Zullino D, Krenz S, Dorogy F, Muller J, et al. Opioid antagonist detoxification under anaesthesia versus traditional clonidine detoxification combined with an additional week of psychosocial support: a randomised clinical trial. *Drug and Alcohol Dependence* 2006;**81**(2):109-16.

Fingerhood 2001 *{published data only}*

Fingerhood MI, Thompson MR, Jasinski DR. A comparison of clonidine and buprenorphine in the outpatient treatment of opiate withdrawal. *Substance Abuse* 2001;**22**(3):193-9.

Friess 1974 *{published data only}*

Friess G. Voluntary detoxification therapy of young drug addicts in a medical clinic. *MMW - Munchener Medizinische Wochenschrift* 1974;**116**(48):2117-20.

Fudala 1989 *{published data only}*

Fudala PJ, Johnson RE, Bunker E. Abrupt withdrawal of buprenorphine following chronic administration. *Clinical Pharmacology & Therapeutics* 1989;**45**(2):186.

Fudala 1998 *{published data only}*

Fudala PJ, Yu E, Macfadden W, Boardman C, Nora Chiang C. Effects of buprenorphine and naloxone in morphine-stabilized opioid addicts. *Drug and Alcohol Dependence* 1998;**50**(1):1-8.

Fudala 2003 *{published data only}*

Fudala PJ, Bridge TP, Herbert S, Williford WO, Chiang CN, Jones K, et al. Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone. *New England Journal of Medicine* 2003;**349**(10):949-58.

Gold 1980 *{published data only}*

Gold MS, Pottash AL, Sweeney DR, Kleber HD. Effect of methadone dosage on clonidine detoxification efficacy. *American Journal of Psychiatry* 1980;**137**(3):375-6.

Gold 1981 *{published data only}*

Gold MS, Pottash ALC, Extein I, Stoll A. Clinical utility of clonidine in opiate withdrawal. *NIDA Research Monograph* 1981;**34**:95-101.

Gonzalez 2015 *{published data only}*

Gonzalez G, DiGirolamo G, Kolodziej ME, Smelson D, Romero-Gonzalez M. Memantine improves buprenorphine treatment for opioid-dependent young adults. *Drug and Alcohol Dependence* 2015;**146**:e124.

Gossop 1986 *{published data only}*

Gossop M, Johns A, Green L. Opiate withdrawal: inpatient versus outpatient programmes and preferred versus random assignment to treatment. *British Medical Journal (Clinical Research Ed)* 1986;**293**(6539):103-4.

Gruber 2008 *{published data only}*

Gruber VA, Delucchi KL, Kielstein A, Batki SL. A randomized trial of 6-month methadone maintenance with standard or minimal counseling versus 21-day methadone detoxification. *Drug and Alcohol Dependence* 2008;**94**(1-3):199-206.

Gunderson 2010 *{published data only}*

Gunderson EW, Wang XQ, Fiellin DA, Bryan B, Levin FR. Unobserved versus observed office buprenorphine/naloxone induction: a pilot randomized clinical trial. *Addictive Behaviors* 2010;**35**(5):537-40.

Howells 2002 *{published data only}*

Howells C, Allen S, Gupta J, Stillwell G, Marsden J, Farrell M. Prison based detoxification for opioid dependence: a randomised double blind controlled trial of lofexidine and methadone. *Drug and Alcohol Dependence* 2002;**67**(2):169-76.

Ivaskevicius 2005 *{published and unpublished data}*

Ivaskevicius J, Jovaisa T, Laurinenas G, Vosylius S, Sipylaite J, Badaras R. Safety and effectiveness of opiate antagonist detoxification under general anesthesia. *Medicina (Kaunas)* 2005;**41**(12):1011-8.

Jimenez-Lerma 2002 *{published data only}*

Jimenez-Lerma JM, Landabaso M, Iraurgi L, Calle R, Sanz J, Gutierrez-Fraile M. Nimodipine in opiate detoxification: a controlled trial. *Addiction* 2002;**97**(7):819-24.

Jittiwutikarn 2004 *{published data only}*

Jittiwutikarn J, Ali R, White JM, Bochner F, Somogyi AA, Foster DJR. Comparison of tincture of opium and methadone to control opioid withdrawal in a Thai treatment centre. *British Journal of Clinical Pharmacology* 2004;**58**(5):536-41.

Johnson 1995a *{published and unpublished data}*

Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence. *Drug and Alcohol Dependence* 1995;**40**(1):17-25.

Johnson 1995b *{published data only}*

Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. Buprenorphine treatment of opioid dependence: clinical trial of daily versus alternate-day dosing. *Drug and Alcohol Dependence* 1995;**40**(1):27-35.

Jovaisa 2006 *{published and unpublished data}*

Jovaisa T, Laurinenas G, Vosylius S, Sipylaite J, Badaras R, Ivaskevicius J. Effects of ketamine on precipitated opiate withdrawal. *Medicina (Kaunas)* 2006;**42**(8):625-34.

Kheirabadi 2011 *{published data only}*

Kheirabadi GR, Salehi M, Maracy MR, Ranjkesh M. Gabapentin in the treatment of opioid withdrawal. *Klinik Psikofarmakoloji Bulteni* 2011;**21**:S116.

Kienbaum 2000 *{published data only}*

Kienbaum P, Scherbaum N, Thurauf N, Michel MC, Gastpar M, Peters J. Acute detoxification of opioid-addicted patients with naloxone during propofol or methohexital anesthesia: a comparison of withdrawal symptoms, neuroendocrine, metabolic, and cardiovascular patterns. *Critical Care Medicine* 2000;**28**(4):969-76.

Klein 2017 *{published data only}*

Klein L, Cole J, Driver B, Martel M. A randomized trial of intramuscular olanzapine versus oral clonidine for symptomatic treatment of opioid withdrawal in the emergency department. *Clinical Toxicology* 2017;**55**(7):692-3.

Kosten 1984 *{published data only}*

Kosten TR, Rounsaville BJ, Kleber HD. Relationship of depression to clonidine detoxification of opiate addicts. *Comprehensive Psychiatry* 1984;**25**(5):503-8.

Kosten 1988 *{published data only}*

Kosten TR, Kleber HD. Buprenorphine detoxification from opioid dependence: a pilot study. *Life Sciences* 1988;**42**(6):635-41.

Kosten 1989 *{published data only}*

Kosten TR, Krystal JH, Charney DS, Price LH, Morgan CH, Kleber HD. Rapid detoxification from opioid dependence. *American Journal of Psychiatry* 1989;**146**(10):1349.

Kour 2012 *{published data only}*

Kour KD. From Modinos' cure to lecithin treatment: detoxification and withdrawal management in the state-

sponsored mass treatment scheme for opium addicts in Assam, 1938-39. *National Medical Journal of India* 2012;**25**(5):296-300.

Liebschutz 2014 *{published and unpublished data}*

Liebschutz JM, Crooks D, Herman D, Anderson B, Tsui J, Meshesha LZ, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. *JAMA Internal Medicine* 2014;**174**(8):1369-76.

Ling 2005 *{published data only}*

Ling W, Amass L, Shoptaw S, Annon JJ, Hillhouse M, Babcock D, et al. A multi-center randomized trial of buprenorphine-naloxone versus clonidine for opioid detoxification: findings from the National Institute on Drug Abuse Clinical Trials Network. *Addiction* 2005;**100**(8):1090-100.

Ling 2009 *{published data only}*

Ling W, Hillhouse M, Domier C, Doraimani G, Hunter J, Thomas C, et al. Buprenorphine tapering schedule and illicit opioid use. *Addiction* 2009;**104**(2):256-65.

Lofwall 2007 *{published data only}*

Lofwall MR, Walsh SL, Bigelow GE, Strain EC. Modest opioid withdrawal suppression efficacy of oral tramadol in humans. *Psychopharmacology* 2007;**194**(3):381-93.

Loimer 1991 *{published data only}*

Loimer N, Linzmayer L, Schmid R, Grunberger J. Similar efficacy of abrupt and gradual opiate detoxification. *American Journal of Drug and Alcohol Abuse* 1991;**17**(3):307-12.

Loimer 1993 *{published data only}*

Loimer N, Hofmann P, Chaudhry H. Ultrashort noninvasive opiate detoxification. *American Journal of Psychiatry* 1993;**150**(5):839.

Malhotra 1997 *{published data only}*

Malhotra A, Basu D, Chintalapudi M, Mattoo SK, Varma VK. Clonidine versus withdrawal using an opioid in inpatient opioid detoxification. *European Addiction Research* 1997;**3**:146-9.

Mannelli 2009a *{published and unpublished data}*

Mannelli P, Patkar AA, Peindl K, Gorelick DA, Wu LT, Gottheil E. Very low dose naltrexone addition in opioid detoxification: a randomized, controlled trial. *Addiction Biology* 2009;**14**(2):204-13.

Mannelli 2009b *{published and unpublished data}*

Mannelli P, Patkar AA, Peindl K, Gottheil E, Wu LT, Gorelick DA. Early outcomes following low dose naltrexone enhancement of opioid detoxification. *American Journal on Addictions* 2009;**18**(2):109-16.

Marsch 2005 *{published and unpublished data}*

Marsch LA, Bickel WK, Badger GJ, Stothart ME, Quesnel KJ, Stanger C, et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. *Archives of General Psychiatry* 2005;**62**(10):1157-64.

McCambridge 2007 *{published and unpublished data}*

McCambridge J, Gossop M, Beswick T, Best D, Bearn J, Rees S, et al. In-patient detoxification procedures, treatment retention, and post-treatment opiate use: comparison of lofexidine plus naloxone, lofexidine plus placebo, and methadone. *Drug and Alcohol Dependence* 2007;**88**(1):91-5.

Mendelson 1999 *{published data only}*

Mendelson J, Jones RT, Welm S, Baggott M, Fernandez I, Melby AK, et al. Buprenorphine and naloxone combinations: the effects of three dose ratios in morphine-stabilized, opiate-dependent volunteers. *Psychopharmacology* 1999;**141**(1):37-46.

Mobasher 2004 *{published and unpublished data}*

Mobasher M, Ziaaddini H, Hamzeii Moghaddam A, Sabzvari F, Sadeghipour S. The effect of gabapentin on withdrawal syndrome, psychiatric disorders and electroencephalogram of opium addicts during the detoxification period. *Iranian Journal of Pharmaceutical Research* 2004;**3**(4):215-23.

Moghadam 2013 *{published data only}*

Moghadam MS, Alavinia M. The effects of gabapentin on methadone based addiction treatment: a randomized controlled trial. *Pakistan Journal of Pharmaceutical Sciences* 2013;**26**(5):985-9.

Montoya 1994 *{published and unpublished data}*

Montoya ID, Mann DJ, Ellison PA, Lange WR, Preston KL. Inpatient medically supervised opioid withdrawal, with buprenorphine alone and in combination with naltrexone. *Clinical Pharmacology & Therapeutics* 1994;**55**(2):131.

Naderi-Heiden 2005 *{published data only}*

Naderi-Heiden A, Frey R, Presslich O, Frottier P, Willinger U, Blasbichler T, et al. Effect of intravenous magnesium sulphate in reducing irritability and restlessness in pure and polysubstance opiate detoxification. *Psychiatry Research* 2005;**135**(1):53-63.

Nasr 2011 *{published data only}*

Nasr DAM, Omran HASA, Hakim SM, Mansour WAA. Ultra-rapid opiate detoxification using dexmedetomidine under general anesthesia. *Journal of Opioid Management* 2011;**7**(5):337-44.

Nigam 1993 *{published and unpublished data}*

Nigam AK, Ray R, Tripathi BM. Buprenorphine in opiate withdrawal: a comparison with clonidine. *Journal of Substance Abuse Treatment* 1993;**10**(4):391-4.

O'Connor 1992 *{published data only}*

O'Connor PG, Waugh ME, Schottenfeld RS, Diakogiannis IA, Rounsaville BJ. Ambulatory opiate detoxification and primary care: a role for the primary care physician. *Journal of General Internal Medicine* 1992;**7**(5):532-4.

O'Connor 1995 *{published data only}*

O'Connor PG, Waugh ME, Carroll KM, Rounsaville BJ, Diagkogiannis IA, Schottenfeld RS. Primary care-based ambulatory opioid detoxification: the results of a clinical trial. *Journal of General Internal Medicine* 1995;**10**(5):255-60.

Oliveto 1998 *{published data only}*

Oliveto AH, Farren C, Kosten TR. Effect of LAAM dose on opiate use in opioid-dependent patients: a pilot study. *American Journal on Addictions* 1998;**7**(4):272-82.

Parran 1994 *{published data only}*

Parran TV Jr, Adelman CL, Jasinski DR. Buprenorphine stabilization and rapid-taper protocol for the detoxification of opioid-dependent patients. *American Journal on Addictions* 1994;**3**(4):306-13.

Perez 2000 *{published data only}*

Perez de los Cobos J, Martin S, Etcheberrigaray A, Trujols J, Batlle F, Tejero A, et al. A controlled trial of daily versus thrice-weekly buprenorphine administration for the treatment of opioid dependence. *Drug and Alcohol Dependence* 2000;**59**(3):223-33.

Resnick 1988 *{published data only}*

Resnick RB, Falk F. Buprenorphine: pilot trials in borderline patients and opiate dependence - treatment of a common disorder?. *NIDA Research Monograph* 1988;**81**:289.

Riordan 1980 *{published data only}*

Riordan CE, Kleber HD. Rapid opiate detoxification with clonidine and naloxone. *Lancet* 1980;**1**(8177):1079-80.

Rosen 1996 *{published data only}*

Rosen MI, Pearsall HR, Woods SW, Kosten TR. The effect of gamma-hydroxybutyric acid on naloxone-precipitated opiate withdrawal. *Neuropsychopharmacology* 1996;**14**(3):187-93.

Rounsaville 1985 *{published data only}*

Rounsaville BJ, Kosten T, Kleber H. Success and failure at outpatient opioid detoxification, evaluating the process of clonidine- and methadone-assisted withdrawal. *Journal of Nervous and Mental Disease* 1985;**173**(2):103-10.

Sam 1990 *{published data only}*

Sam L, Cami J, Fernandez T, Olle JM, Peri JM, Torrens M. Double blind assessment of buprenorphine withdrawal in opiate-addicts. *NIDA Research Monograph Series* 1990;**105**:455.

Sanders 2013 *{published data only}*

Sanders NC, Mancino MJ, Gentry WB, Guise JB, Bickel WK, Thostenson J, et al. Randomized, placebo-controlled pilot trial of gabapentin during an outpatient, buprenorphine-assisted detoxification procedure. *Experimental and Clinical Psychopharmacology* 2013;**21**(4):294-302.

Seifert 2005 *{published data only}*

Seifert J, Metzner C, Paetzold W, Borsutzky M, Ohlmeier M, Passie T, et al. Mood and affect during detoxification of opiate addicts: a comparison of buprenorphine versus methadone. *Addiction Biology* 2005;**10**(2):157-64.

Senay 1983 *{unpublished data only}*

Senay E, Tennant FS, Washton AM. Boehringer Ingelheim GmbH report number U85-0844. Boehringer Ingelheim Pty Ltd 1983.

Shi 1993 *{published and unpublished data}*

Shi JM, O'Connor PG, Constantino JA, Carroll KM, Schottenfeld RS, Rounsaville BJ. Three methods of ambulatory opiate detoxification: preliminary results of a randomized clinical trial. *NIDA Research Monograph Series* 1993;**132**:309.

Shohrati 2009 *{published data only}*

Shohrati M, Almasi V, Shajiei A, Nekouhesh l, Najafian B, Naghizadeh MM. N-acetyl cysteine effect on life quality of morphine addicts in treatment period: a pilot study. *Kowsar Medical Journal* 2009;**13**(4):297-301.

Shohrati 2010 *{published data only}*

Shohrati M, Shajiei A, Nekouhesh L, Almasi V, Naghizadeh M, Ghanei M. N-acetyl cysteine effect on sleep quality and respiratory function of morphine addicts in treatment period: a pilot study. *Journal of Military Medicine* 2010;**11**(4):197-201.

Sigmon 2004 *{published data only}*

Sigmon SC, Wong CJ, Chausmer AL, Liebson IA, Bigelow GE. Evaluation of an injection depot formulation of buprenorphine: placebo comparison. *Addiction* 2004;**99**(11):1439-49.

Sinha 2007 *{published data only}*

Sinha R, Kimmerling A, Doebrick C, Kosten TR. Effects of lofexidine on stress-induced and cue-induced opioid craving and opioid abstinence rates: preliminary findings. *Psychopharmacology* 2007;**190**(4):569-74.

Specker 1998 *{published data only}*

Specker S, Wananukul W, Hatsukami D, Nolin K, Hooke L, Kreek MJ, et al. Effects of dynorphin A(1-13) on opiate withdrawal in humans. *Psychopharmacology* 1998;**137**(4):326-32.

Srisurapanont 1998 *{published data only}*

Srisurapanont M, Jarusuraisin N. Lorazepam in the treatment of opiate-withdrawal insomnia: a randomized double-blind study. *Acta Psychiatrica Scandinavica* 1998;**97**(3):233-5.

Strain 2011 *{published data only}*

Strain EC, Harrison JA, Bigelow GE. Induction of opioid-dependent individuals onto buprenorphine and buprenorphine/naloxone soluble-films. *Clinical Pharmacology and Therapeutics* 2011;**89**(3):443-9.

Strang 1990 *{published data only}*

Strang J, Gossop M. Comparison of linear versus inverse exponential methadone reduction curves in the detoxification of opiate addicts. *Addictive Behaviors* 1990;**15**(6):541-7.

Strang 2017 *{published data only}*

Strang J, Reed K, Bogdanowicz K, Bell J, Van Der Waal R, Keen J, et al. Randomised comparison of a novel buprenorphine oral lyophilisate versus existing buprenorphine sublingual tablets in opioid-dependent patients: a first-in-patient phase II randomised open label safety study. *European Addiction Research* 2017;**23**(2):61-70.

Subramaniam 2011 *{published and unpublished data}*

Subramaniam GA, Warden D, Minhajuddin A, Fishman MJ, Stitzer ML, Adinoff B, et al. Predictors of abstinence: National Institute of Drug Abuse multisite buprenorphine/naloxone treatment trial in opioid-dependent youth. *Journal of the American Academy of Child and Adolescent Psychiatry* 2011;**50**(11):1120-8.

Sullivan 2017 *{published and unpublished data}*

Sullivan M, Bisaga A, Pavlicova M, Choi CJ, Mishlen K, Carpenter KM, et al. Long-acting injectable naltrexone induction: a randomized trial of outpatient opioid detoxification with naltrexone versus buprenorphine. *American Journal of Psychiatry* 2017;**174**(5):459-67.

Telias 2000 *{published data only}*

Telias D, Nir-Hod J. Buprenorphine-ketorolac vs. clonidine-naproxen in the withdrawal from opioids. *International Journal of Psychosocial Rehabilitation* 2000;**4**(4):441-6.

Umbricht 1999 *{published data only}*

Umbricht A, Montoya ID, Hoover DR, Demuth KL, Chiang CT, Preston KL. Naltrexone shortened opioid detoxification with buprenorphine. *Drug and Alcohol Dependence* 1999;**56**(3):181-90.

Umbricht-Schneiter 1996 *{published and unpublished data}*

Umbricht-Schneiter A, Montoya ID, Demuth KL, Preston KL. Opioid detoxification with buprenorphine alone or in combination with naltrexone. *NIDA Research Monograph* 1996;**162**:117.

Vining 1988 *{published data only}*

Vining E, Kosten TR, Kleber HD. Clinical utility of rapid clonidine-naltrexone detoxification for opioid abusers. *British Journal of Addiction* 1988;**83**(5):567-75.

Walsh 2003 *{published data only}*

Walsh SL, Strain EC, Bigelow GE. Evaluation of the effects of lofexidine and clonidine on naloxone-precipitated withdrawal in opioid-dependent humans. *Addiction* 2003;**98**(4):427-39.

Wang 1996 *{published data only}*

Wang RI, Young LD. Double-blind controlled detoxification from buprenorphine. *NIDA Research Monograph* 1996;**162**:114.

Washton 1979 *{published data only}*

Washton AM, Resnick RB, Rowson RA. Clonidine hydrochloride: a non opiate treatment for opiate withdrawal. *NIDA Research Monograph* 1979;**27**:233-9.

Washton 1980 *{published data only}*

Washton AM, Resnick RB. Clonidine versus methadone for opiate detoxification. *Lancet (London, England)* 1980;**2**(8207):1297.

Washton 1981 *{published data only}*

Washton AM, Resnick RB. Clonidine vs. methadone for opiate detoxification: double-blind outpatient trials. *NIDA Research Monograph* 1981;**34**:89-94.

White 2001 *{published data only}*

White R, Alcorn R, Feinmann C. Two methods of community detoxification from opiates: an open-label comparison of lofexidine and buprenorphine. *Drug and Alcohol Dependence* 2001;**65**(1):77-83.

Wilcox 2013 *{published and unpublished data}*

Wilcox CE, Bogenschutz MP, Nakazawa M, Woody G. Concordance between self-report and urine drug screen data in adolescent opioid dependent clinical trial participants. *Addictive Behaviors* 2013;**38**(10):2568-74.

Wilson 1993 *{published data only}*

Wilson RS, DiGeorge WS. Methadone combined with clonidine versus clonidine alone in opiate detoxification. *Journal of Substance Abuse Treatment* 1993;**10**(6):529-35.

Woody 2008 *{published and unpublished data}*

Woody GE, Poole SA, Subramaniam G, Dugosh K, Bogenschutz M, Abbott P, et al. Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth: a randomized trial. *JAMA* 2008;**300**(17):2003-11.

Wylie 1995 *{published data only}*

Wylie AS, Stewart AM. Lofexidine based regimen for opiate addicts. *British Journal of General Practice* 1995;**45**(393):217-8.

Yu 2008 *{published data only}*

Yu E, Miotto K, Akerele E, Montgomery A, Elkashef A, Walsh R, et al. A Phase 3 placebo-controlled, double-blind, multi-site trial of the alpha-2-adrenergic agonist, lofexidine, for opioid withdrawal. *Drug and Alcohol Dependence* 2008;**97**(1-2):158-68.

Zarghami 2012 *{published data only}*

Zarghami M, Masoum B, Shiran MR. Tramadol versus methadone for treatment of opiate withdrawal: a double-blind, randomized, clinical trial. *Journal of Addictive Diseases* 2012;**31**(2):112-7.

Ziaaddini 2009 *{published and unpublished data}*

Ziaaddini H, Qahestani A, Moin Vaziri M. Comparing symptoms of withdrawal, rapid detoxification and detoxification with clonidine in drug dependent patients. *Addiction & Health* 2009;**1**(2):63-8.

Ziaaddini 2015 *{published and unpublished data}*

Ziaaddini H, Ziaaddini A, Asghari N, Nakhaee N, Eslami M. Trial of tramadol plus gabapentin for opioid detoxification. *Iranian Red Crescent Medical Journal* 2015;**17**(1):1-5.

Ziedonis 2009 *{published data only}*

Ziedonis DM, Amass L, Steinberg M, Woody G, Krejci J, Annon JJ, et al. Predictors of outcome for short-term medically supervised opioid withdrawal during a randomized, multicenter trial of buprenorphine-naloxone and clonidine in the NIDA clinical trials network drug and alcohol dependence. *Drug and Alcohol Dependence* 2009;**99**(1-3):28-36.

References to studies awaiting assessment

Huertas 1995 *{published data only}*

Huertas D, Lopez-Gomez I, Chamorro L, Martin M. New combined treatment for opioid detoxification: the association between dextropropoxyphene and guanfacine [Nueva pauta combinada para la desintoxicacion de opiaceos: la linea DG]. *Revista de Psiquiatria de la Facultad de Medicina de Barcelona* 1995;**22**(5):109-13.

Johnson 1992 *{published data only}*

Johnson RE, Fudala PJ, Cheskin LR. A comparison of buprenorphine to clonidine for rapid inpatient opiate detoxification. *Clinical Pharmacology & Therapeutics* 1992;**51**(2):167.

Kang 2002 *{published data only}*

Kang L, Li J, Huang MS. Random double blind test study of detoxicated effect of Kangfuxin, Fukangpian & clonidine hydrochloride on opiate withdrawal syndromes. *Chinese Journal of Clinical Rehabilitation* 2002;**6**(23):3586-7.

Rezaiyan 2014 *{published and unpublished data}*

Rezaiyan MK, Moghadam HK, Khosrojerdi H, Afshari R. Very low-dose naltrexone versus placebo in alleviating withdrawal manifestation. *Clinical Toxicology* 2014;**52**:368.

Steinmann 2008 *{published data only}*

Steinmann C, Artmann S, Schachtschneider A, Paul HW. Methadone versus buprenorphine for inpatient detoxification treatment. *Sucht* 2008;**54**(4):217-21.

Additional references

Afghanistan Counter Narcotics & UNODC 2005

Afghanistan Ministry of Counter Narcotics & United Nations Office on Drugs and Crime. Afghanistan drug use survey 2005: Executive summary. 2005.

Ahmadi 2004

Ahmadi J, Babaee-Beigi M, Alishahi M, Maany I, Hidari T. Twelve-month maintenance treatment of opium-dependent patients. *Journal of Substance Abuse Treatment* 2004;**26**(1):363-6.

Amato 2013

Amato L, Davoli M, Ferri M, Ali R. Methadone at tapered doses for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2013, Issue 2. [DOI: 10.1002/14651858.CD003409.pub4]

Amin-Esmaeili 2016

Amin-Esmaeili M, Rahimi-Movaghar A, Sharifi V, Hajebi A, Radgoodarzi R, Mojtabai R, et al. Epidemiology of illicit drug use disorders in Iran: prevalence, correlates, comorbidity and service utilization, results from the Iranian mental health survey. *Addiction* 2016;**111**:1836-47. [DOI: 10.1111/add.13453]

Brunton 2006

Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th Edition. New York (NY): McGraw-Hill, 2006.

Chaturvedi 2013

Chaturvedi HK, Mahanta J, Bajpai RC, Pandey A. Correlates of opium use: retrospective analysis of a survey of tribal communities in Arunachal Pradesh, India. *BMC Public Health* 2013;**13**:325.

Ghaffarnejad 2009

Ghaffarnejad A, Ziaadini H, Banazadeh N. Comparative evaluation of psychiatric disorders in opium and heroin dependent patients. *Addiction and Health* 2009;**1(1)**:20-4.

Gowing 2009a

Gowing L, Ali R, White JM. Buprenorphine for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD002025.pub4]

Gowing 2009b

Gowing L, Ali R, White JM. Opioid antagonists with minimal sedation for opioid withdrawal. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD002021.pub3]

Gowing 2010

Gowing L, Ali R, White JM. Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD002022.pub3]

Gowing 2014

Gowing L, Farrell M, Ali R, White JM. Alpha2-adrenergic agonists for the management of opioid withdrawal. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD002024.pub4]

GRADE 2004

Oxman AD, GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(19):1490-4.

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**(7560):924-6.

Guyatt 2011

Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines 1. Introduction - GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology* 2011;**64**(4):383-94.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Iranian MoH 2002

Iranian MoH. Epidemiologic study of drug abuse in Iran. Tehran. Iranian Ministry of Health 2002.

Jafari 2010

Jafari S, Rahimi-Movaghar A, Craib KJP, Baharlou S, Mathias R. A follow-up study of drug users in Southern Iran. *Addiction Research & Theory* 2010;**18**(1):59-70.

Menati 2016

Menati W, Valizadeh R, Menati R, Niazi M, Nazarzadeh M, Bidel Z. Determination of opium abuse prevalence in Iranian young people: a systematic review and meta-analysis. *Journal of Substance Use* 2017;**22**:3-10.

PubChem 2008

PubChem. Thebaine. PubChem Substance and Compound databases 2008. [PubChem Identifier: SID 134971785URL: https://pubchem.ncbi.nlm.nih.gov/substance/134971785]

Rahimi-Movaghar 2006

Rahimi-Movaghar A, Izadian E, Yunesian M. Drug use situation in university students in Iran: a literature review. *Payesh [Health Monitor]* 2006;**5**:83-104.

Rahimi-Movaghar 2013

Rahimi-Movaghar A, Amin-Esmaeili M, Hefazi M, Yousefi-Nooraie R. Pharmacological therapies for maintenance treatments of opium dependence. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD007775.pub2]

Rahimi-Movaghar 2015

Rahimi-Movaghar A, Amin-Esmaeili M, Safarcherati A, Sarami H, Rafiey H. A scientometric study of Iranian scientific productions in the field of substance use and addiction research in the years 2008 to 2012. *Addiction & Health* 2015;**7**(3-4):99-108.

Ray 2004

Ray R. The extent, pattern and trends of drug abuse in India: national survey. India. Ministry of Social Justice and Empowerment, United Nations Office on Drugs and Crime. Regional Office for South Asia, 2004.

Ray 2006

Ray R, Kattimani S, Sharma HK. Opium abuse and its management: global scenario. Department of Mental Health and Substance Abuse Management, World Health Organization, AND National Drug Dependence Treatment Centre, All India Institute of Medical Sciences, New Delhi, India, 2006.

Razaghi 1999

Razaghi EM, Rahimi-Movaghar A, Hosseini M, Mohammad K, Madani S. Rapid situation assessment of drug abuse in Iran. Tehran: Iranian Welfare Organization & United Nations International Drug Control Program (UNDCP), 1999:18.

RevMan 2014 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, 2014.

Schünemann 2006

Schünemann HJ, Jaeschke R, Cook D, Bria W, El-Solh A, Ernst A, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. *American Journal of Respiratory and Critical Care Medicine* 2006;**174**(5):605-14.

Sweetman 2007

Sweetman S. In: Sean C Sweetman BPharm FRPharmS editor(s). Martindale: The Complete Drug Reference. London: Pharmaceutical Press, 2007. [ISBN 0-85369-687-X]

UNODC 2010

United Nations Office on Drugs and Crime. Drug use in Afghanistan 2009 survey: executive summary. www.unodc.org/documents/data-and-analysis/Studies/Afghan-Drug-Survey-2009-Executive-Summary-web.pdf (accessed prior to 25 May 2018).

UNODC 2011

United Nations Office on Drugs and Crime. World Drug Report 2011. Vienna: United Nations Publications, 2011.

Westermeyer 1977

Westermeyer J, Peng G. Opium and heroin addicts in Laos. II. A study of matched pairs. *Journal of Nervous and Mental Disease* 1977;**164**(5):351-4.

WHO/EMRO 2004

World Health Organization, Regional Office for the Eastern Mediterranean. A draft of the 5-year regional strategic planning on substance abuse, 2005-2009. 2004.

World Health Organization 2009

World Health Organization. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence. Geneva: World Health Organization, 2009.

Yamazoe 1981

Yamazoe Y, Numata H, Yanagita T. Thebaine metabolites in the urine of rhesus monkeys. *Japanese Journal of Pharmacology* 1981;**31**(3):433-42.

Zarghami 2008

Zarghami M. Is methadone substitution the best treatment of choice for opioid dependence?. *Iranian Journal of Psychiatry and Behavioral Sciences* 2008;**2**(2):1-4.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ahmadi Abhari 2003

Methods	**Design:** controlled clinical trial (claimed as double-blind randomised controlled trial) **Study setting:** outpatient clinic **Number of study centres and location:** 1, Tehran, Iran
Participants	66 opioid dependent by DSM-IV; 90% using opium and 10% using heroin **Group sizes:** 32 in baclofen group, 34 in clonidine group **Gender:** 65 male and 1 female **Age:** 18 to 60 **History:** Mean (±SD) duration of opioid use: 5.84 (±4.93) years No difference between groups in age, other demographic characteristics and duration of opioid use **Exclusion criteria:** pregnancy; breastfeeding; systolic blood pressure of less than 90 mmHg; serious physical illness; history of psychosis, mania, severe major depression, antisocial personality disorder, or mental retardation; concurrent dependence on alcohol, cocaine, cannabis, or hallucinogens
Interventions	(1) baclofen, initial dose 15 mg/day, increased to 40 mg/day until day 4 and maintained until day 10. Then tapered over 4 days. 3-daily divided doses (2) clonidine, initial dose 0.3 mg/day, increased to 0.8 mg/day until day 4 and maintained until day 10. Then tapered over 4 days. 3-daily divided doses
Outcomes	Number completed treatment (completed 14 days of treatment and negative urine test for morphine at day 14) Mean days in treatment Mean withdrawal score (by Short Opioid Withdrawal Scale, 10-item plus diarrhoea); mean mental withdrawal symptoms (5-item), mean total physical and mental symptoms (graph) Severity of adverse effects (23-item questionnaire) at days 0, 1, 2, 3, 4, 7, and 14 (graph) Depression (by HDRS) and anxiety (by HARS) at days 0, 7, and 14
Notes	From 66 participants, 90% were opium dependents. It is unclear whether withdrawal symptoms and side effects were rated by observers or participants. Full text published in Persian (most review authors fully understand Persian), abstract in English. Source of funding not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assignment is non-random. Quote: "Subjects were allocated alternately to Baclofen and clonidine group."
Allocation concealment (selection bias)	High risk	Allocation concealment not done.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	For objective outcomes: Blinding of participants and personnel probably not done. Outcomes are highly prone to bias.

Ahmadi Abhari 2003 *(Continued)*

Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of participants and personnel probably not done. Outcomes are highly prone to bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessment probably not done. However, assessment of the objective outcome (number of participants who completed treatment) is unlikely to be affected by non-blinding of personnel or participants.
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of outcome assessment probably not done, therefore assessment of the withdrawal scores is highly prone to bias.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Amiri 2014

Methods	**Design:** controlled clinical trial (claimed as double-blind randomised controlled trial) **Study setting:** inpatient **Number of study centres and location:** 1, Tehran, Iran
Participants	69 opioid dependents by DSM-IV-TR; all opium users **Group sizes:** 35 in clonidine group, 34 in clonidine plus amantadine group **Gender:** male **Age**: 20 to 40 There was no significant difference in age and initial withdrawal symptoms at admission time between groups. **Exclusion criteria:** psychotic symptoms and history or current physical/general medical illness, i.e. all conditions requiring immediate treatment or added risk for individuals who were supposed to tolerate adrenergic symptoms (e.g. diabetes mellitus, hepatic and renal insufficiency, creatinine ≥ 1.2 mg/dL and Alanine transaminase (ALT) ≥ 40 IU)
Interventions	(1) clonidine: clonidine tablet 0.4 to 1.2 mg/day according to the participant's tolerance in 3 divided doses. Mean dose of clonidine was 0.9 ± 0.3. (2) clonidine plus amantadine: clonidine tablet 0.4 to 1.2 mg/day according to the participant's tolerance in 3 divided doses, plus amantadine capsule 100 mg every 12 hours. Mean dose of clonidine was 0.8 ± 0.4.

Amiri 2014 *(Continued)*

	Both groups received clonazepam tablet 1 mg every 8 hours and acetaminophen tablet 500 mg every 6 hours.
Outcomes	Number of participants who completed 3-day treatment Mean score of withdrawal symptoms (by COWS, 11 symptoms) at 24, 48, 72 hours after initiation of treatment
Notes	Withdrawal symptoms were assessed by physicians. The study is funded by Clinical Psychiatry Research Center, Tabriz, Iran.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process. Quote: "The patients who were admitted to the hospital and fulfilled the inclusion criteria were randomly assigned into two groups."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	For objective outcomes: Blinding of participants not done. Outcomes are highly prone to bias. Quote: “The second group received all of the medications described above plus amantadine capsule 100 mg each 12 hours.” “All of the medications were selected from available preparations from the same company.”
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of participants not done. Outcomes are highly prone to bias. Quote: “The second group received all of the medications described above plus amantadine capsule 100 mg each 12 hours.” “All of the medications were selected from available preparations from the same company.”
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessor probably not done. However, assessment of the objective outcome (number of participants who completed treatment) is unlikely to be affected by non-blinding of assessors.
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of outcome assessor probably not done. Quote: "The second group received all of the medications described above plus amantadine capsule 100 mg each 12 hours." "All of the medications were selected from available preparations from the same company." Assessment of the withdrawal scores is highly prone to bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "From the total of 69 participants, 60 patients completed the trial." "group 1, day 1: severe symptoms, withdrawn by family, hypotension (n = 3), day 2: non compliance (n = 2), group 2, day 1: severe symptoms, non compliance (n = 2), day 2: non compliance (n = 2)"
Selective reporting (reporting bias)	Low risk	No selective reporting

Amiri 2014 *(Continued)*

		Quote: "This trial is registered with the Iranian Clinical Trials Registry (IRCT 201207196972N2)"
Other bias	Low risk	None apparent

Kheirabadi 2008

Methods	**Design:** double-blind randomised controlled trial **Study setting:** outpatient clinic **Number of study centres and location:** 1, Isfahan, Iran
Participants	40 opium dependent by DSM-IV **Group sizes**: 20 in methadone group, 20 in methadone + gabapentin group **Gender:** 37 male and 3 female **Age:** 21 to 61 Route of administration: smoking Duration of opium dependence: at least 1 year No significant difference between groups in age, dose of methadone and other medications, and mean withdrawal score at baseline **Exclusion criteria:** history of other illicit drug use or psychiatric medication in 2 months before study, any other major psychiatric disorder, significant concurrent medical illness, organic brain disorder, mental retardation, pregnancy or breastfeeding
Interventions	(1) methadone + gabapentin: gabapentin 300 mg/day on day 1, increased 300 mg/day and reached to 900 mg/day on day 3, which was maintained until end of trial on day 21. Methadone was prescribed at a 20 to 65 mg/day based on the amount of opium used in the last month prior to study and was adjusted based on withdrawal symptoms and signs after cessation of opium for the first 3 days. It was reduced by 7.5% of initial dosage/day during the following 14 days. Methadone was stopped on day 18. (2) methadone: methadone was prescribed as in group 1. Both groups could receive symptomatic medications (i.e. clonidine, oxazepam, or trazodone) if required.
Outcomes	Number of participants who completed treatment (defined as number of participants still in treatment at day 18) Mean withdrawal score (by Subjective Opiate Withdrawal Scale, 16-item) at days 3, 7, 10, 14, and 18, and mean score of each of 16 items over 5 assessments. Withdrawal symptoms were rated by the participants.
Notes	Source of funding: Isfahan University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement

Kheirabadi 2008 *(Continued)*

Random sequence generation (selection bias)	Low risk	A randomisation automated system on a 1-to-1 basis was used for randomisation.
Allocation concealment (selection bias)	Low risk	Quote: "During the study, the randomisation list was held securely, and released only after study completion."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Quote: “Gabapentin and placebo were dispensed in identical appearing capsules. Patients who were randomised to the placebo group took the same number of capsules as those who were assigned to the treatment group.” “This trial was a 3-week double-blind, randomised, placebo-controlled trial.”
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Quote: “Gabapentin and placebo were dispensed in identical appearing capsules. Patients who were randomised to the placebo group took the same number of capsules as those who were assigned to the treatment group.” “This trial was a 3-week double-blind, randomised, placebo-controlled trial.”
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessor was done. Quote: "During the study, the randomisation list was held securely, and released only after study completion." "This trial was a 3-week double-blind, randomised, placebo-controlled trial."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of outcome assessor was done. Quote: "During the study, the randomisation list was held securely, and released only after study completion." "This trial was a 3-week double-blind, randomised, placebo-controlled trial."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One patient in the placebo group was excluded at day 14 and two others were excluded at day 17 because of noncompliance with the scheduled treatment programme and self-medication with illicit and/or over-the-counter (OTC) drugs."
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Lal 1976

Methods	**Design:** controlled clinical trial (claimed as randomised controlled trial) **Study setting:** inpatient **Number of study centres and location:** 1, Patiala, India
Participants	20 opium dependents

Lal 1976 *(Continued)*

	Group size: 10 (gradual reduction of methadone), 10 (stable dose and sudden withdrawal of methadone) **Gender:** male **Age:** 22 to 70 (mean = 41) No significant difference between groups in demographic characteristics (age, marital status, occupation, religion, and education), use of other substances, and average daily opium use Participants were not excluded for use of other substances.
Interventions	Inpatient 15-day program: (1) gradual reduction of methadone: flexible stabilising daily methadone dose based on level of opium intake, reduced by approximately 20% every alternate day and stopped on day 10 (range of methadone dose in stabilised dose: 10 to 20 mg/day, mean of 14.5, given in 2 divided doses) (2) stable dose and sudden withdrawal of methadone: flexible stabilising daily methadone dose based on level of opium intake, maintained for 10 days and then abruptly withdrawn completely on day 11 (range of methadone dose in stabilised dose: 10 to 30 mg/day, mean of 16.0, given in 2 divided doses) Both groups received 300 mg aspirin twice a day.
Outcomes	Number of participants who complained of withdrawal symptoms during treatment Number of participants with each complaint (body aches and pain, insomnia, rhinorrhoea, diarrhoea, nervousness and tremor, spontaneous ejaculation)
Notes	Source of funding not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process Quote: “The patients were randomly assigned to one of two treatment groups: Group A (standard procedure) and Group B (sudden withdrawal)."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants was done. Quote: "The drug was given in identical powders mixed with powdered aspirin, 300 mg twice a day" However, no objective outcome was assessed in this study.
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants was done. Quote: "The drug was given in identical powders mixed with powdered aspirin, 300 mg twice a day"
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: No information provided for blinding of outcome assessor. However, no objective outcome was assessed in this study.

Lal 1976 *(Continued)*

Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Unclear risk	For subjective outcomes: No information provided for blinding of outcome assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing or loss to follow-up
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Salehi 2005

Methods	**Design:** controlled clinical trial **Study setting:** outpatient followed by inpatient treatment **Number of study centres and location:** 1, Isfahan, Iran
Participants	44 opium dependents by DSM-IV-TR **Group sizes:** 22 in methadone plus amitriptyline group, 22 in methadone group **Gender:** male **Age:** 18 to 60 No injecting drug user Demographic characteristics (age, education, marital status, and employment) and methadone doses of the 2 groups were not significantly different. **Exclusion criteria:** severe physical illness, history of psychosis or mania, suicidal or homicidal thoughts, pregnancy, or multisubstance dependence (except nicotine). Dropout due to severe adverse effect was reported as an exclusion criterion.
Interventions	(1) methadone plus amitriptyline: 3 days of methadone in doses that controlled the subjective and objective withdrawal symptoms and signs, decreased by 10% each day from day 4 and discontinued on day 14. Amitriptyline 25 mg was started from day 4 and continued for 1 week, increased to 50 mg (in 2 divided doses) for another week. (2) methadone: methadone was prescribed as in group 1. From day 4, participants in both groups received clonidine 0.3 mg/day (in 3 divided doses) for 1 week and 0.6 mg/day (in 3 divided doses) for another week. From day 19, participants in both groups were hospitalised for 3 days and received naloxone every day for 3 to 5 hours (0.8 mg, 1.6 mg, 2.4 mg from days 1 to 3 of hospitalisation, respectively).
Outcomes	Mean withdrawal score (by 10-item Short Opioid Withdrawal Scale) and mean mental withdrawal score (by 5-item checklist) and a total withdrawal score (Short Opioid Withdrawal Scale score + mental score + diarrhoea) at days 7, 15, 17, and 25 Mean pain score (by 15-item MPQ) at days 7, 15, 17, and 25

Salehi 2005 *(Continued)*

	Completion rate defined as completing 25 days of treatment and negative urine test for opium at the end. However, the results of completion rate were not reported. We contacted the authors, but received no response.
Notes	The assessments were done by an assessor. The profession of the assessors is not reported. Full text published in Persian (most review authors fully understand Persian), abstract in English. Source of funding: Research Center for Behavioral Sciences, Isfahan University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "Subjects were assigned to each study group based on their order of presence to the study"
Allocation concealment (selection bias)	High risk	Allocation concealment was not done.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants was done. Quote: “Placebo tablets were identical to amitriptyline tablets.”
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants was done. Quote: “Placebo tablets were similar to amitriptyline tablets.”
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessment was done. Quote: "Assessment of patients was done by assessor unaware of the assigned intervention."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of outcome assessment was done. Quote: "Assessment of patients was done by assessor unaware of the assigned intervention."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided.
Selective reporting (reporting bias)	High risk	Completion of treatment in the 25 days was not reported. Assessment of mean total withdrawal score (Short Opioid Withdrawal Scale score + mental score + diarrhoea) at days 7, 15, 17, and 25 was mentioned in the methods but not reported in the results.
Other bias	Low risk	None apparent

Salehi 2007a

Methods	**Design:** controlled clinical trial **Study setting:** outpatient **Number of study centres and location:** 2, Arak, Iran
Participants	76 opium dependents by DSM-IV (from 89 opium dependents who entered treatment; data on 76 who completed treatment at the end of week 8 were analysed) **Group sizes:** 38 in buprenorphine group, 38 in clonidine group **Gender:** 67 male and 9 female **Age:** < 40 First detoxification attempt; daily opium use of ≤ 2 g; duration of dependence of < 1 year; no other substance use No statistically significant difference between groups in sex, marital status, and daily opium dose **Exclusion criteria:** pregnancy, blood pressure of ≥ 140/90 mmHg. In addition, dropout from the detoxification process or positive urine test for morphine during detoxification was considered an exclusion criterion.
Interventions	(1) buprenorphine: intramuscular injection of 0.3 mg on day 1, 0.6 mg on day 2, 0.9 mg on day 3. Then tapered by 0.2 mg each day and was completely discontinued on day 10. (2) clonidine: tablet of 0.1 mg on days 1 and 2, 0.2 mg on day 3, 0.4 mg on day 4, in 3 divided doses. Then tapered every other day by 0.1 mg each day and completely discontinued on day 10. Both groups received sodium diclofenac (25 mg twice a day) and amitriptyline (25 mg 3 times a day).
Outcomes	Analysis was based on 76/89 participants who completed 10 days of treatment. Number of severe withdrawal symptoms at days 1 to 10 (method of assessment not reported) Number of participants with adverse effects at days 1 to 10: hypotension (not defined), headache, sedation, dizziness, dry mouth, nausea, constipation, and sweating
Notes	It is unclear who assessed withdrawal symptoms. Full text published in Persian (most review authors fully understand Persian), abstract in English. Source of funding was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assignment is non-random. Quote: "Subjects were allocated alternately to group A and B by a general practitioner, a member of the research team."
Allocation concealment (selection bias)	High risk	Allocation concealment was not done.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants and personnel was done. Quote: “The patients were received three brown tablets consisting of 500 milligram starch as placebo.” “a

Salehi 2007a *(Continued)*

		syringe containing 1 cc sterile water were injected to gluteal muscle as placebo."
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants and personnel was done. Quote: "The patients were received three brown tablets consisting of 500 milligram starch as placebo." "a syringe containing 10 cc sterile water were injected to gluteal muscle as placebo."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessment was probably done. Quote: "This parallel, randomised and double blind clinical trial was conducted in 2005."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of outcome assessment was probably done. Quote: "This parallel, randomised and double blind clinical trial was conducted in 2005."
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Among 89 participants, 4 patients dropped out because of hypotension (BP < 90/60 mmHg), and 9 patients (7 from clonidine and 2 from buprenorphine group) did not complete the detoxification period or did not come for urine tests and dropped out from the study after 4 and 8 weeks." These 13 participants were not considered in the analysis, even in assessment of relapse and low blood pressure as an adverse effect of medication.
Selective reporting (reporting bias)	High risk	Completion rate as a key outcome was not reported.
Other bias	Low risk	None apparent

Salehi 2007b

Methods	**Design:** controlled clinical trial (claimed as randomised controlled trial) **Study setting:** not reported **Number of study centres and location:** 1, Isfahan, Iran
Participants	72 opium dependents based on DSM-IV **Group sizes:** 37 in methadone group, 35 in tramadol group **Gender:** male **Age:** 20 to 60 Had no objective signs of opioid withdrawal when used 15 mg methadone for 1 day No significant differences between groups in age, marital status, duration of drug abuse, and baseline Short Opioid Withdrawal Scale

Salehi 2007b *(Continued)*

	Exclusion criteria: presence of any medical illness that prohibited administration of methadone and tramadol, taking extra medications, polysubstance dependence, presence of any major psychiatric disorder such as bipolar disorder, psychosis, and major depressive disorder
Interventions	(1) methadone, 15 mg/day reduced by 15% every day to reach zero at day 7 and placebo for another week (2) tramadol, 450 mg/day reduced by 15% every day to reach zero at day 7 and placebo for another week Both groups received clonidine 0.3 mg/day and oxazepam 10 to 30 mg/day.
Outcomes	Number of participants who completed treatment Mean withdrawal score (by Short Opioid Withdrawal Scale (SOWS), 16-item) and mean mental score of SOWS, both at days 1, 3, 5, 7, 9, 11, 13, 15 Mean score for each of 5 mental symptoms of SOWS at days 1, 3, 5, 7, 14 Side effects score at days 7 and 14, including somnolence, sweating, dizziness, nausea, vomiting, and constipation
Notes	The assessor was a psychiatric resident. Source of funding was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process Quote: "These patients were randomly assigned into two groups for a double blind clinical trial."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants was done. Quote: "Doses of opioids were given by same number of capsules with identical shape and size twice daily for three stabilization days." "Neither patients, nor researchers knew the contents of capsules."
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants was done. Quote: "Doses of opioids were given by same number of capsules with identical shape and size twice daily for three stabilization days." "Neither patients, nor researchers knew the contents of capsules."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessors was done. Quote: "Neither patients, nor researchers knew the contents of capsules."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of outcome assessors was done.

Salehi 2007b *(Continued)*

		Quote: "Neither patients, nor researchers knew the contents of capsules."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information about reasons for dropout Quote: "Fourteen patients in group A and 12 in group B were dropped out through the course of study."
Selective reporting (reporting bias)	High risk	There are errors in reporting, e.g. the difference between the 2 groups in mean mental score at day 15 has been reported as significant, but it is insignificant.
Other bias	Low risk	None apparent

Satija 1988

Methods	**Design:** controlled clinical trial **Study setting:** inpatient **Number of study centres and location:** 1, Jodhpur, India
Participants	102 opium dependents diagnosed by ICD-9 criteria **Gender:** male **Group size**: 3 arms: 34 (high-dose clonidine), 34 (low-dose clonidine), 34 (symptomatic therapy) **Age:** 20 to 65 No significant differences among groups in age, dose and duration of opium intake **Exclusion criteria:** psychotic conditions; current use of monoamine oxidase inhibitors, neuroleptics, sedatives hypnotics, antihypertensive drugs; current alcohol abuse; allergy to imidazolidine drugs; any medical diseases such as chronic cardiac, renal, metabolic diseases, and moderate to severe hypertension
Interventions	(1) high-dose clonidine: starting with 0.5 mg/day and increased to 1 to 1.2 mg/day until symptoms were controlled (2) low-dose clonidine: starting with 0.1 mg/day and increased to 0.5 to 0.6 mg/day during 3 to 5 days and maintained during next 10 days (3) symptomatic therapy: chlorpromazine (150 mg/day), nitrazepam (10 mg at bedtime), antiemetics, analgesics, and other symptomatic therapy as needed All groups received pharmacotherapy for 2 weeks and were hospitalised for 3 weeks.
Outcomes	Number of participants who completed treatment Mean withdrawal score for 24 symptoms (by 24-item Withdrawal Symptoms Rating Scale, rated by an independent psychiatrist) at the end of week 1 and 2. Withdrawal symptoms were compared at the end of week 2 with the symptoms at the end of week 1 in each of the 3 groups. Number of participants with hypotension and associated tachycardia as adverse effect (no definition for hypotension was provided)
Notes	Withdrawal symptoms were rated by an independent psychiatrist. For each withdrawal symptom, a score of 0 to 3 was given, but the maximum score for each symptom reported in the results was 50.8.

Satija 1988 *(Continued)*

Source of funding was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information about random allocation Quote: "All the subjects were male and they were divided into group A, B and C (34 patients in each group)."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	For objective outcomes: Blinding of participants and personnel was probably not done. Outcomes are highly prone to bias. Quote: "Group A was given clonidine (small dose) 0.1 mg on the 1st day and gradually increased to 0.5 mg - 0.6 mg during the following 3-5 days. This dose is maintained during next 10 days. Group B was given symptomatic therapy which included chlorpromazine (150 mg/day), nitrazepam (10 mg bed time), antiemetics, analgesics and other symptomatic therapy as needed. Group C was given clonidine (high doses) 0.5 mg to start with and increased to 1 mg - 1.2 mg/day till symptoms were controlled." "The drugs were given in identical capsules and patients and evaluating doctor did not know about the drugs patient was taking."
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of participants and personnel was probably not done. Outcomes are highly prone to bias. Quote: "Group A was given clonidine (small dose) 0.1 mg on the 1st day and gradually increased to 0.5 mg - 0.6 mg during the following 3-5 days. This dose is maintained during next 10 days. Group B was given symptomatic therapy which included chlorpromazine (150 mg/day), nitrazepam (10 mg bed time), antiemetics, analgesics and other symptomatic therapy as needed. Group C was given clonidine (high doses) 0.5 mg to start with and increased to 1 mg - 1.2 mg/day till symptoms were controlled." "The drugs were given in identical capsules and patients and evaluating doctor did not know about the drugs patient was taking."
Blinding of outcome assessment (detection bias) Objective outcomes	High risk	For objective outcomes: Blinding of assessors was probably not done. Assessment of 1 of the objective outcomes (number of participants who completed treatment) is unlikely to be affected by non-blinding of the assessors, but hypotension (another objective outcome) might be prone to high risk of bias.
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of assessors was probably not done, therefore assessment of the withdrawal scores is highly prone to bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants who dropped out of the study or left the study was equal among the three groups.
Selective reporting (reporting bias)	Low risk	None apparent

Satija 1988 *(Continued)*

Other bias	Low risk	None apparent

Singh 1984

Methods	**Design:** controlled clinical trial (claimed as randomised controlled trial) **Study setting:** not reported **Number of study centres and location:** 1, Patiala, India
Participants	105 opium dependents **Group sizes (those who completed treatment)**: 22 (low-dose diphenoxylate), 24 (high-dose diphenoxylate), 24 (low-dose dextro-propoxyphene), 20 (high-dose dextro-propoxyphene) The study was conducted in 2 phases on different groups of participants. In phase 1, the first 2 interventions of low-dose regimens were provided; in phase 2, the last 2 interventions of high-dose regimens were provided. **Gender:** male **Age**: 20 to 58 The 4 groups were merged into 2 groups of diphenoxylate and propoxyphene for comparison. It was reported that the groups after completion were similar in terms of age, marital status, occupation, religion, education, and type and amount of narcotic drugs. **Exclusion criteria:** multiple addictions or other gross psychiatric illnesses
Interventions	(1) low-dose diphenoxylate: 20 to 40 mg based on daily opium consumption (e.g. up to 250 mg/day, 250 to 500 mg/day, and higher than 500 mg/day of morphine were given 20 mg/day, 30 mg/day, and 40 mg/day of diphenoxylate, respectively) (2) high-dose diphenoxylate: 40 to 80 mg in divided dose, based on daily opium consumption (3) low-dose dextro-propoxyphene: 400 to 800 mg based on daily opium consumption (e.g. up to 250 mg/day, 250 to 500 mg/day, and higher than 500 mg/day of morphine were given 400 mg/day, 600 mg/day, and 800 mg/day of dextro-propoxyphene, respectively) (4) high-dose dextro-propoxyphene: 800 to 1600 mg/day in divided doses, based on daily opium consumption The dose was adjusted for the first 48 hours and then maintained at the same level for 10 days. Then suddenly withdrawn at day 11 and followed by placebo for 3 days. In a few cases the initial calculated dose had to be adjusted "because of the fact that the patient did not give an accurate estimate of amount of narcotics consumed by him or because of varying potency available in the market." Mild hypnotic (e.g. diazepam or nitrazepam) was given to participants of the 4 groups at bedtime.
Outcomes	Number of participants with each of 8 withdrawal symptoms (probably in 10 days): body aches and pains (mild and severe), insomnia, rhinorrhoea or sneezing, diarrhoea, nervousness or tremors, nausea and retching, anorexia, lacrimation Side effects in 10 days
Notes	The assessors of the withdrawal symptoms were not reported. Source of funding: Messers Ranbaxy Limited and Searle Company Limited provided medications. No other funding source is reported.

Singh 1984 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomisation was done between each 2 groups and not the 4 groups. Insufficient information about the sequence generation process between groups A and B Quote: "In each phase of the study, participants were randomly allocated to two treatment groups A and B."
Allocation concealment (selection bias)	High risk	No information provided. Concealment was probably done for type of medication, but not for dose of medication.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: No objective outcome was reported.
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of participants was probably done for type of medication, but not for dose of medication. Quote: "The drugs were administered by nurses on double blind basis in identical capsules, each capsule containing either 5 mg of diphenoxylate or 100 mg of propoxyphene." All outcomes are highly prone to bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: No objective outcome was reported.
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of assessors was probably done for type of medication, but not for dose of medication. Since mainly subjective outcomes have been assessed, the assessment is highly prone to bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	No information about number of dropouts in each group is provided. Quote: "15 patients out of 105 (14%) dropped out during the course of the study or attempted to smuggle in drugs clandestinely or were suspected to be taking narcotics during the treatment period and hence were removed from the study."
Selective reporting (reporting bias)	High risk	Completion rate was not reported for each group.
Other bias	Low risk	None apparent

Somogyi 2008

Methods	**Design:** controlled clinical trial (claimed as randomised controlled trial) **Study setting:** not reported **Number of study centres and location:** 1, Chiang Mai, Thailand

Somogyi 2008 *(Continued)*

Participants	45 opium dependents; 13 out of 45 participants had data errors and incomplete blood sample. The information on 32 participants who completed the requirements of the interdosing study was analysed and provided. **Group sizes (those who completed treatment):** 13 (10 mL of tincture of opium), 8 (20 mL of tincture of opium), 11 (30 mL of tincture of opium) **Gender:** 31 male and 1 female **Age:** 18 to 53 There were differences between groups for prior daily opium use. There were no differences between groups for age and body weight. No exclusion criteria were reported. No participants had significant medical illnesses, none were taking other medications that alter pharmacokinetic of morphine, and none were pregnant or breastfeeding.
Interventions	1) 10 mL of TOP mixture (6.66 mg morphine equivalents) twice daily 2) 20 mL of TOP mixture (13.3 mg morphine equivalents) twice daily 3) 30 mL of TOP mixture (20 mg morphine equivalents) twice daily Those participants who used a relatively small amount of opium prior to treatment initiation experienced sedation when given 20 to 30 mL TOP, and so were allocated to the lower-dosage group for safety reasons.
Outcomes	Mean withdrawal score by self report 16-item Methadone Symptoms Checklist at day 5 (0, 1, 3, and 8 hours after TOP dose) Adverse effects, including effects on blood pressure, respiratory rate, and heart rate
Notes	Source of funding: the investigators' institutions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	2 different explanations for allocation of participants to groups are reported: 1) "Initially, the participants were randomly allocated to the following three different groups." 2) "Forty-five opium-dependent Thai participants were allocated to three dosing groups depending on their self-reported prior opium use." Random selection was probably not done.
Allocation concealment (selection bias)	High risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	For objective outcomes: Blinding of participants was not done, therefore outcomes are highly prone to bias. “This open-label study ...”
Blinding of participants and personnel (performance bias) for subjective outcomes	High risk	For subjective outcomes: Blinding of participants was not done, therefore outcomes are highly prone to bias. “This open-label study ...”

Somogyi 2008 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) Objective outcomes	High risk	For objective outcomes: Blinding of outcome assessor was not done. Objective outcomes such as blood pressure and heart rate are highly prone to bias. “This open-label study ...”
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of outcome assessor was not done. Results for all outcomes are highly prone to bias.“This open-label study ...”
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: “In total 32 subjects completed the requirements of the interdosing study, with transcription errors and incomplete blood samples occurring in 13 of the original 45 subjects.” No more information provided. Intention-to-treat analysis: unclear
Selective reporting (reporting bias)	High risk	Completion rate was not reported for each group.
Other bias	Low risk	None apparent

Tabassomi 2016

Methods	**Design:** double-blind randomised controlled trial **Study setting:** outpatient clinic of a psychiatric hospital **Number of study centres and location:** 1, Sari, Iran
Participants	74 opium dependent by DSM-IV **Group sizes:** 35 (opium tincture), 39 (methadone) **Gender:** male **Age:** 18 to 60 Mean duration of opium dependence: 4.8 years No significant difference between groups in age, marital status, duration of addiction, and ASI score **Exclusion criteria:** clinically significant physical illnesses, any psychiatric illnesses, and using other drugs or substances except nicotine
Interventions	Participants’ severity of dependence was assessed by the ASI, and they were categorised to mild, moderate or severe blocks. (1) opium tincture: 45, 90, and 135 mg/day depending on severity of addiction (2) methadone: 15, 30, and 45 mg/day depending on severity of addiction The total dose of opium tincture or methadone syrup was divided into 2 equal doses and administered twice a day for all participants. The starting doses were maintained for 5 consecutive days, and then detoxification was initiated by tapered dose reductions (20% every day) over a period of 5 days, to reach abstinence. At the end of the 10th day the medications were discontinued.
Outcomes	Number of participants who completed treatment (defined as number of participants still in treatment at day 10)

Tabassomi 2016 *(Continued)*

	Number of participants with each of 9 adverse effects (probably in 10 days): headache, dizziness, sleepiness, misbalance, constipation, nausea, perspiration, tension, and respiratory depression Mean withdrawal score for each of 10 days of detoxification and the total mean withdrawal score for all 10 days (by 13-item OOWS) (graphs)
Notes	Source of funding: Mazandaran University of Medical Sciences

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomisation by a computer-generated list.
Allocation concealment (selection bias)	Low risk	"Each patient received either OT (group A) or methadone syrup (group B) by a nurse who was blind to the study groups, according to the computer generated list."
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants was done. Quote: "Appearance, color, and odor of both medications were matched by pharmaceutical industry experts. ... double-blind conditions in which neither the patient, nor the medical staff (attending physician, resident, and nurse), were aware of the study group assignment."
Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants was done. Quote: "Appearance, color, and odor of both medications were matched by pharmaceutical industry experts. ... double-blind conditions in which neither the patient, nor the medical staff (attending physician, resident, and nurse), were aware of the study group assignment."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Quote: "Assessments were done by a resident who was blind to group assignment."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of participants was done. Quote: "Appearance, color, and odor of both medications were matched by pharmaceutical industry experts. ... double-blind conditions in which neither the patient, nor the medical staff (attending physician, resident, and nurse), were aware of the study group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	None apparent
Other bias	Low risk	None apparent

Taraghi 2005

Methods	**Design:** controlled clinical trial (claimed as randomised controlled trial) **Study setting:** outpatient **Number of study centres and location:** 2, Tabriz, Iran
Participants	361 opium dependents by DSM-IV **Group sizes:** 120 in clonidine group, 241 in methadone group **Gender:** not reported **Age:** 19 to 70 Duration of opium use of at least 1 year, at least 2.3 g of opium by oral use or 4.7 g by smoking No significant differences between groups in sex, age, education, marital status, and duration of drug use. Using opium by oral route was significantly more frequent in the methadone group ($P < 0.01$). No exclusion criteria
Interventions	(1) clonidine: 0.2 to 1.2 mg (in divided doses/day) based on age, weight, and clinical situation for 3 to 5 days. 3 days after completion of treatment with clonidine, naloxone challenge test was done and oral naltrexone (50 mg) was started. (2) methadone: 25 to 45 mg (in divided doses/day) based on age, weight, and clinical situation and tapered in 12 to 25 days. 1 week after completion of treatment with methadone, naloxone challenge test was done and oral naltrexone (50 mg) was started. Both groups received benzodiazepines, SSRIs, TCAs, NSAIDs, vitamins if needed.
Outcomes	Number of participants who completed treatment Severity of each of 10 assessed withdrawal symptoms evaluated by a psychologist Client satisfaction (The characteristics of the questionnaires, the time of assessment, and the number of those who were assessed were not reported.)
Notes	Full text published in Persian (most review authors fully understand Persian), abstract in English. Source of funding was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process Quote: "120 participants were randomly assigned to clonidine group and 241 to methadone group."
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	High risk	For objective outcomes: Blinding of participants and personnel not done. Outcomes are highly prone to bias.

Taraghi 2005 *(Continued)*

Blinding of participants and personnel (performance bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of participants and personnel not done. Outcomes are highly prone to bias.
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessors not done. However, the objective outcome (completion of treatment) is unlikely to have been affected by non-blinding of outcome assessor.
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	High risk	For subjective outcomes: Blinding of outcome assessors not done. The subjective outcomes are highly prone to bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "In the primary stages, 161 patients left the detoxification program." 20 participants from the clonidine group and 141 participants from the methadone group. The reasons for and times of dropouts were not reported. Since there was considerable dropout, especially in the methadone group, some key outcomes like adverse effects have been reported only for those who completed the treatment.
Selective reporting (reporting bias)	High risk	There are several errors in reporting. Below are some examples. • The results on withdrawal and satisfaction were reported for 100 individuals from each group. • The rates presented for patient satisfaction in each group are not matched with the reported for significance of difference (P value).
Other bias	Low risk	None apparent

Ziaaddini 2012

Methods	**Design:** controlled clinical trial (claimed as randomised) **Study setting:** inpatient **Number of study centres and location:** 1, Kerman, Iran
Participants	35 opioid dependents by DSM-IV. Contact with authors revealed that all participants were opium dependents. **Group sizes:** 14 in buprenorphine group, 21 in clonidine group **Gender:** male **Age:** 18 to 40 First detoxification attempt No statistically significant difference between groups in age **Exclusion criteria:** serious medical conditions (such as acute hepatitis and diabetes), acute psychotic disease, personality disorder, concomitant abuse of methadone, beta-blockers, or calcium channel blockers, any medical condition interfering with clonidine (such as cardiovascular and renal disease),

Ziaaddini 2012 *(Continued)*

	a history of allergy to clonidine, buprenorphine, or naltrexone. In addition, individuals with blood pressure < 90/60 mmHg and pulse rate < 60 beats/minute during treatment were excluded from the study.
Interventions	(1) buprenorphine: 2 mg sublingual tablets of buprenorphine hydrochloride were used. On days 1 to 5, 2, 4, 6, 4, and 2 mg/day buprenorphine were used, respectively. Depending on the severity of symptoms, in some cases 2 to 4 mg buprenorphine were added. (2) clonidine: 0.2 mg on day 1, 0.6 mg in 3 divided doses on days 2 and 3, 0.2 mg on days 4 and 5. Moreover, 0.2 to 0.4 mg/day of clonidine was administered if indicated. To ensure the success of detoxification, participants received naltrexone 2 days following end of detoxification. They were then discharged while prescribed with 25 mg/day naltrexone for 6 months. Both groups could receive trazodone, lorazepam, hydroxyzine, paracetamol, and hyoscine if required; however, it is unclear whether these medications were prescribed during inpatient detoxification or after discharge.
Outcomes	Number of those who successfully completed treatment, defined by receiving naltrexone 2 days after the end of the detoxification phase and before discharge Mean withdrawal score (by COWS, 11-item and ARWS, 16-item) at days 1, 2, 3, and 5 Mean substance craving score (by a VAS) at days 1, 2, 3, and 5 Number of those who remained on naltrexone maintenance treatment within 6-month follow-up period
Notes	COWS was rated by a psychiatric resident, and ARWS and VAS were rated by participants. Supported by Neuroscience Research Center, Kerman, Iran

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process Quote: “Participants were randomly allocated to either clonidine or buprenorphine detoxification group." “In the clonidine group, 71.4% of the subjects were employed, 33.3% were married, and only 8.4% had university education. In the buprenorphine group, 42.9% of patients were employed, 35.7% were married, and 14.3% had university education (P > 0.05).” The 2 groups were probably not comparable at baseline.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) objective outcomes	Low risk	For objective outcomes: Blinding of participants and personnel was done. Quote: ”To ensure blinding, the placebo of each drug was also prepared by the Department of Pharmacology of Kerman University of Medical Sciences (Kerman, Iran).” “All drugs and placebos were assigned a code and kept by a person who was not involved in the study.”
Blinding of participants and personnel (performance bias) for subjective outcomes	Low risk	For subjective outcomes: Blinding of participants and personnel was done.

Ziaaddini 2012 *(Continued)*

All outcomes		Quote: "To ensure blinding, the placebo of each drug was also prepared by the Department of Pharmacology of Kerman University of Medical Sciences (Kerman, Iran)." "All drugs and placebos were assigned a code and kept by a person who was not involved in the study."
Blinding of outcome assessment (detection bias) Objective outcomes	Low risk	For objective outcomes: Blinding of outcome assessor was done. Quote: "All drugs and placebos were assigned a code and kept by a person who was not involved in the study."
Blinding of outcome assessment (detection bias) for subjective outcomes All outcomes	Low risk	For subjective outcomes: Blinding of outcome assessor was done. Some scales were rated by participants, who were also blinded. Quote: "All drugs and placebos were assigned a code and kept by a person who was not involved in the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "In one case, clonidine was discontinued on the second day due to blood pressure below 90/60 mmHg."
Selective reporting (reporting bias)	High risk	The rate of positive urinary samples for opioids at the end of 6 months was reported as 1 of the main outcomes of the study, but the results are unclear. Side effects were assessed, but not reported. Four other outcome measures have been reported: (1) number who received maintenance treatment, (2) mean days in maintenance therapy, (3) number who received naltrexone maintenance, and (4) mean days stayed on naltrexone medication. The definition of maintenance treatment in the first two outcomes (apart from naltrexone maintenance in the outcomes 3 and 4) is unclear.
Other bias	Low risk	None apparent.

ARWS: Adjective Rating Withdrawal Scale
ASI: Addiction Severity Index
COWS: Clinical Opioid Withdrawal Scale
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
HARS: Hamilton Anxiety Rating Scale
HDRS: Hamilton Depression Rating Scale
ICD-9: International Statistical Classification of Diseases and Related Health Problems, 9th Revision
MPQ: McGill Pain Questionnaire
NSAIDs: non-steroidal anti-inflammatory drugs
OOWS: Objective Opioid Withdrawal Scale
SD: standard deviation
SSRIs: selective serotonin reuptake inhibitors
TCAs: tricyclic antidepressants
VAS: visual analogue scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Akhondzadeh 2000	It was not clear if any opium dependent was included in the study. We contacted the author but received no response.
Alam 2001	The study was not a controlled clinical trial.
Ansari 2007	The study was not a controlled clinical trial.
Assadi 2004	13 out of 40 participants were opium dependent. We contacted the author, and data for opium dependents were not available.
Badiei 2005	27 out of 54 participants were opium dependent. We contacted the author, and data for opium dependents were not available.
Bearn 1996	None of the participants were opium dependent.
Bearn 2001	We contacted the author, and none of the participants were opium dependent.
Becker 2001	None of the participants were opium dependent.
Bertschy 1997	None of the participants were opium dependent.
Beswick 2003	None of the participants were opium dependent.
Bisaga 1997	None of the participants were opium dependent. The study was not a controlled clinical trial.
Brewer 1998	None of the participants were opium dependent. The study was not a controlled clinical trial.
Bruce 1964	No results for outcomes were provided.
Buntwal 2000	None of the participants were opium dependent.
Carnwath 1998	None of the participants were opium dependent.
Curran 2001	None of the participants were opium dependent.
De Jong 2005	None of the participants were opium dependent. Compared general anaesthesia with no anaesthesia. The pharmacologic treatments were similar in the groups.
Dunn 2015	None of the participants were opium dependent.
Eftekhar 2005	The study was not a controlled clinical trial.
Erlendson 2017	The participants were not opioid dependent.
Espinosa 2001	None of the participants were opium dependent.
Favrat 2006	We contacted the author, and none of the participants were opium dependent.
Fingerhood 2001	We contacted the author, and none of the participants were opium dependent.
Friess 1974	None of the participants were opium dependent. The study was not a controlled clinical trial.
Fudala 1989	None of the participants were opium dependent. The study was not a controlled clinical trial.
Fudala 1998	None of the participants were opium dependent.

Study	Reason for exclusion
Fudala 2003	None of the participants were opium dependent.
Gold 1980	None of the participants were opium dependent. The study was not a controlled clinical trial.
Gold 1981	None of the participants were opium dependent. The study was not a controlled clinical trial.
Gonzalez 2015	None of the participants were opium dependent.
Gossop 1986	None of the participants were opium dependent. The same interventions were provided in different settings.
Gruber 2008	None of the participants were opium dependent.
Gunderson 2010	None of the participants were opium dependent. The same interventions were provided by different methods.
Howells 2002	None of the participants were opium dependent.
Ivaskevicius 2005	We contacted the author, and none of the participants were opium dependent. The study was not a controlled clinical trial.
Jimenez-Lerma 2002	None of the participants were opium dependent.
Jittiwutikarn 2004	The study was not a controlled clinical trial.
Johnson 1995a	We contacted the author, and none of the participants were opium dependent.
Johnson 1995b	None of the participants were opium dependent.
Jovaisa 2006	We contacted the author, and none of the participants were opium dependent. ¸Different protocols for anaesthesia were compared.
Kheirabadi 2011	The study was not a controlled clinical trial.
Kienbaum 2000	None of the participants were opium dependent. Different protocols for anaesthesia were compared.
Klein 2017	The study assessed 1-hour treatment of opioid withdrawal in emergency rooms.
Kosten 1984	None of the participants were opium dependent.
Kosten 1988	None of the participants were opium dependent.
Kosten 1989	None of the participants were opium dependent.
Kour 2012	The study was not a controlled clinical trial.
Liebschutz 2014	We contacted the author, and none of the participants were opium dependent. The study was not a controlled clinical trial.
Ling 2005	None of the participants were opium dependent.
Ling 2009	None of the participants were opium dependent.
Lofwall 2007	None of the participants were opium dependent.

Study	Reason for exclusion
Loimer 1991	None of the participants were opium dependent.
Loimer 1993	None of the participants were opium dependent. The study was not a controlled clinical trial.
Malhotra 1997	None of the participants were opium dependent.
Mannelli 2009a	We contacted the author, and none of the participants were opium dependent.
Mannelli 2009b	We contacted the author, and none of the participants were opium dependent.
Marsch 2005	We contacted the author, and none of the participants were opium dependent.
McCambridge 2007	We contacted the author, and none of the participants were opium dependent.
Mendelson 1999	None of the participants were opium dependent.
Mobasher 2004	We contacted the author for the number of opium dependents in each group. 33 out of 71 participants were opium dependent. Data on opium dependents were not available.
Moghadam 2013	The study is about maintenance treatment.
Montoya 1994	We contacted the author, and none of the participants were opium dependent.
Naderi-Heiden 2005	The study is about efficacy of intravenous magnesium sulphate.
Nasr 2011	The study compared different protocols of anaesthesia in ultra-rapid detoxification.
Nigam 1993	10% of the participants were opium dependent. We contacted the author, and data for opium dependents were not available.
O'Connor 1992	None of the participants were opium dependent.
O'Connor 1995	None of the participants were opium dependent.
Oliveto 1998	None of the participants were opium dependent.
Parran 1994	None of the participants were opium dependent.
Perez 2000	None of the participants were opium dependent.
Resnick 1988	The study was not a controlled clinical trial.
Riordan 1980	None of the participants were opium dependent.
Rosen 1996	None of the participants were opium dependent.
Rounsaville 1985	None of the participants were opium dependent.
Sam 1990	None of the participants were opium dependent.
Sanders 2013	None of the participants were opium dependent.
Seifert 2005	None of the participants were opium dependent.
Senay 1983	None of the participants were opium dependent.

Study	Reason for exclusion
Shi 1993	We contacted the author, and none of the participants were opium dependent.
Shohrati 2010	Number of opium dependents is not reported. We contacted the author, but did not receive data.
Shohrati 2009	Number of opium dependents is not reported. We contacted the author, but did not receive data.
Sigmon 2004	None of the participants were opium dependent.
Sinha 2007	None of the participants were opium dependent. The interventions were provided after 4 weeks of detoxification.
Specker 1998	None of the participants were opium dependent.
Srisurapanont 1998	We contacted the author, and none of the participants were opium dependent.
Strain 2011	None of the participants were opium dependent.
Strang 1990	None of the participants were opium dependent.
Strang 2017	The study was on maintenance treatment.
Subramaniam 2011	We contacted the author, and none of the participants were opium dependent. The study investigated the difference between buprenorphine maintenance and buprenorphine detoxification.
Sullivan 2017	We contacted the author, and none of the participants were opium dependent.
Telias 2000	None of the participants were opium dependent.
Umbricht 1999	None of the participants were opium dependent.
Umbricht-Schneiter 1996	We contacted the author, and none of the participants were opium dependent.
Vining 1988	None of the participants were opium dependent. The study evaluated 2 of the same regimens of antagonist-induced withdrawal, differing in day on which naltrexone was administered (day 2 or 3).
Walsh 2003	None of the participants were opium dependent.
Wang 1996	None of the participants were opium dependent.
Washton 1981	None of the participants were opium dependent.
Washton 1979	None of the participants were opium dependent.
Washton 1980	None of the participants were opium dependent.
White 2001	None of the participants were opium dependent.
Wilcox 2013	We contacted the author, and none of the participants were opium dependent.
Wilson 1993	The study was not a controlled clinical trial.
Woody 2008	We contacted the author, and none of the participants were opium dependent.
Wylie 1995	None of the participants were opium dependent. The study was not a controlled clinical trial.

Study	Reason for exclusion
Yu 2008	None of the participants were opium dependent.
Zarghami 2012	None of the participants were opium dependent.
Ziaaddini 2009	14 of 30 participants were opium dependents. We contacted the author, and data for opium dependents were not available.
Ziaaddini 2015	39 of 59 participants were opium dependents. We contacted the author, and data for opium dependents were not available.
Ziedonis 2009	None of the participants were opium dependent.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Huertas 1995

Methods	Controlled clinical trial
Participants	Data not available
Interventions	(1) guanfacine (2) guanfacine and propoxyphene
Outcomes	Data not available
Notes	Abstract and full text are in Spanish and are not available.

Johnson 1992

Methods	Controlled clinical trial Setting: inpatient Country: USA
Participants	16 opiate dependents Group sizes: (1) 8, (2) 8
Interventions	(1) buprenorphine: sublingual for 3 days (2) clonidine: oral for 5 days
Outcomes	Signs and symptoms of withdrawal
Notes	The document is an abstract. It is unclear whether there were opium dependents in the trial or not. We were unable to contact the authors.

Kang 2002

Methods	Controlled clinical trial
Participants	120 participants Group sizes: (1) 33, (2) 28, (3) 30, (4) 29
Interventions	(1) Kangfuxin (2) Fukang Pian (3) clonidine hydrochloride (4) placebo
Outcomes	Withdrawal symptoms Anxiety Adverse effects
Notes	It is unclear whether there were opium dependents in the trial or not. We were unable to contact the authors.

Rezaiyan 2014

Methods	Controlled clinical trial
Participants	64 opioid dependents
Interventions	(1) very low-dose naltrexone (2) placebo Both received clonidine.
Outcomes	Completion of treatment Withdrawal symptoms Craving
Notes	The paper is an abstract. We contacted the author, and opium dependents were included. The full text is under review. The authors were not willing to share data before publishing the results.

Steinmann 2008

Methods	Randomised controlled trial Setting: inpatient Country: Germany
Participants	60 opiate dependents Group sizes: (1) 30, (2) 30
Interventions	(1) methadone

Steinmann 2008 *(Continued)*

	(2) buprenorphine
Outcomes	Completion of treatment Withdrawal symptoms Craving Use of additional medication
Notes	It is unclear whether there were opium dependents in the trial or not. We were unable to contact the authors. The abstract is in English; full text is in German and is not available.

DATA AND ANALYSES

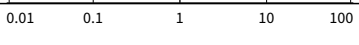
Comparison 1. Pharmacological detoxification treatment versus other pharmacological detoxification treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Completion of treatment	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Baclofen versus clonidine	1	66	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.63, 1.80]
1.2 Clonidine versus clonidine plus amantadine	1	69	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.24]
1.3 Clonidine versus buprenorphine, inpatient setting	1	35	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.20]
1.4 Clonidine versus methadone	1	361	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.69, 2.38]
1.5 Methadone versus tramadol	1	72	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.37]
1.6 Methadone versus methadone plus gabapentin	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.96, 1.43]
1.7 Tincture of opium versus methadone	1	74	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.95, 1.05]
2 Withdrawal symptoms at day 3	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Clonidine versus clonidine plus amantadine	1	60	Mean Difference (IV, Fixed, 95% CI)	-3.56 [-5.97, -1.15]
2.2 Clonidine versus buprenorphine, inpatient setting	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-2.93, 0.13]

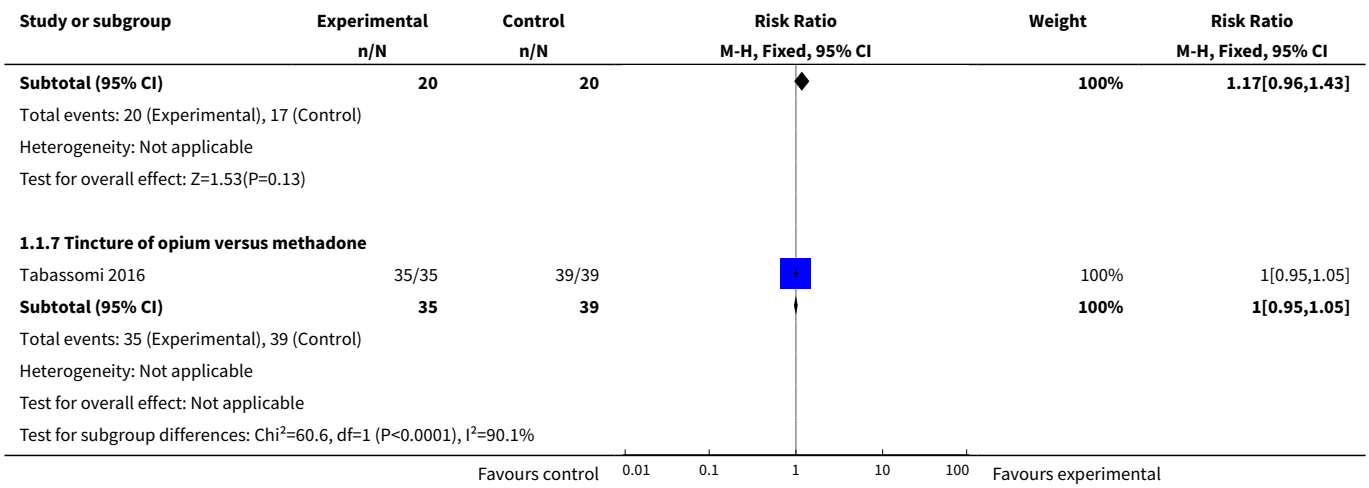
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Methadone versus tramadol	1	72	Mean Difference (IV, Fixed, 95% CI)	0.04 [-2.68, 2.76]
2.4 Methadone versus methadone plus gabapentin	1	40	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-6.72, 2.32]

Analysis 1.1. Comparison 1 Pharmacological detoxification treatment versus other pharmacological detoxification treatment, Outcome 1 Completion of treatment.

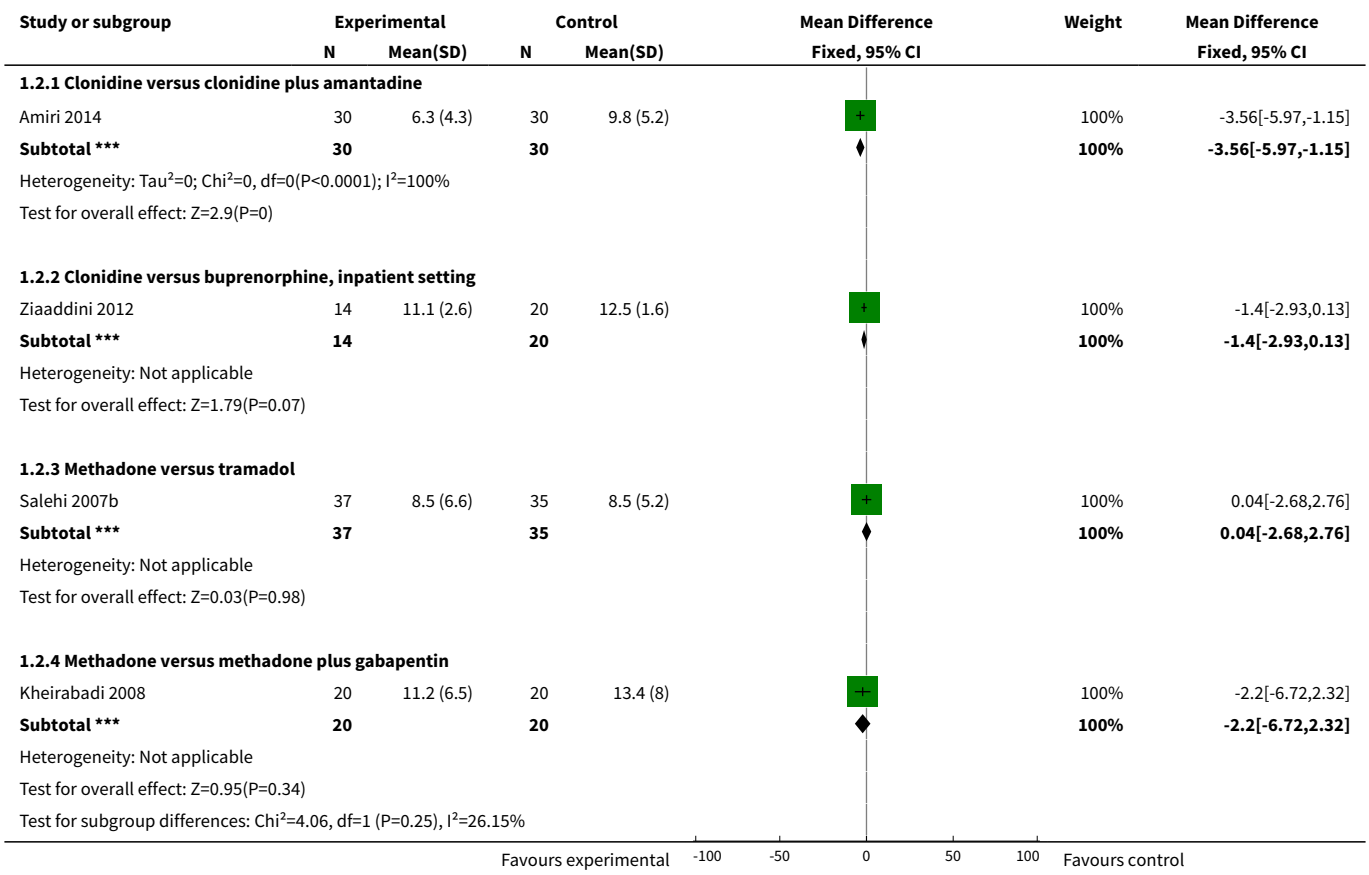
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Baclofen versus clonidine					
Ahmadi Abhari 2003	15/32	15/34		100%	1.06[0.63,1.8]
Subtotal (95% CI)	**32**	**34**		**100%**	**1.06[0.63,1.8]**
Total events: 15 (Experimental), 15 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.22(P=0.82)					
1.1.2 Clonidine versus clonidine plus amantadine					
Amiri 2014	30/34	30/35		100%	1.03[0.86,1.24]
Subtotal (95% CI)	**34**	**35**		**100%**	**1.03[0.86,1.24]**
Total events: 30 (Experimental), 30 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
1.1.3 Clonidine versus buprenorphine, inpatient setting					
Ziaaddini 2012	14/14	20/21		100%	1.04[0.9,1.2]
Subtotal (95% CI)	**14**	**21**		**100%**	**1.04[0.9,1.2]**
Total events: 14 (Experimental), 20 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
1.1.4 Clonidine versus methadone					
Taraghi 2005	100/120	100/241		100%	2.01[1.69,2.38]
Subtotal (95% CI)	**120**	**241**		**100%**	**2.01[1.69,2.38]**
Total events: 100 (Experimental), 100 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=8.04(P<0.0001)					
1.1.5 Methadone versus tramadol					
Salehi 2007b	22/37	22/35		100%	0.95[0.65,1.37]
Subtotal (95% CI)	**37**	**35**		**100%**	**0.95[0.65,1.37]**
Total events: 22 (Experimental), 22 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.77)					
1.1.6 Methadone versus methadone plus gabapentin					
Kheirabadi 2008	20/20	17/20		100%	1.17[0.96,1.43]



Favours control — Favours experimental



Analysis 1.2. Comparison 1 Pharmacological detoxification treatment versus other pharmacological detoxification treatment, Outcome 2 Withdrawal symptoms at day 3.



APPENDICES

Appendix 1. Search strategies and results

DATABASE SEARCHED: MEDLINE

Period searched: 1966 to September 2017

Last searched: 13 September 2017

Items	N° records
#1. exp substance withdrawal syndrome/ or exp metabolic detoxication, drug/	29,438
#2. (detoxify* or desintoxi* or disintoxi* or withdraw*).tw.	120,446
#3. 1 or 2	134,225
#4. opium.tw.	2,128
#5. exp opium/	1,987
#6.poppy straw.tw.	228
#7.4 or 5 or 6	3,267
#8. 3 and 7	221
#9. randomized controlled trial.pt.	480,594
#10. controlled clinical trial.pt.	96,827
#11. randomized.tw.	442,177
#12. placebo.tw.	198,683
#13. drug therapy.fs.	2,059,637
#14. random*.tw.	961,992
#15. trial.tw.	506,861
#16. groups.tw.	1,786,704
#17. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	4,433,918
#18. (Humans not (humans and animals)).sh.	15,557,092
#19. 17 and 18	3,109,114
#20. 8 and 19	95

DATABASE SEARCHED: Embase

Period searched: 1974 to September 2017

Last searched: 13 September 2017

Items	N° records
#1. 'withdrawal syndrome'/exp	36,383
#2. 'drug detoxification'/exp	4,260
#3. ((drug OR substance) NEXT/2 (abuse* OR addict* OR dependen*)):ab,ti	73,845
#4. detoxify*:ab,ti OR desintoxi*:ab,ti OR disintoxi*:ab,ti OR withdraw*:ab,ti	157,482
#5. #1 OR #2 OR #3 OR #4	246,883
#6. opium:ab,ti	2,668
#7. 'poppy straw'	50
#8. poppy:ab,ti AND straw:ab,ti	56
#9. 'opiate'/exp	65,825
#10. #6 OR #7 OR #8 OR #9	66,877
#11. #5 AND #10	9,533
#12. random*:ab,ti	1,213,337
#13. factorial*:ab,ti	30,887
#14. crossover*:ab,ti	62,689
#15. cross:ab,ti	744,863
#16. placebo*:ab,ti	258,114
#17. (doubl* NEXT/2 blind*):ab,ti	180,742
#18. (singl* NEXT/2 blind*):ab,ti	20,300
#19. assign*:ab,ti	317,479
#20. allocat*:ab,ti	117,923
#21. volunteer*:ab,ti	222,764
#22. 'crossover-procedure'/exp	52,412
#23. 'randomized controlled trial'/exp	463,362
#24. 'single-blind procedure'/exp	29,178
#25. #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	2,526,975

(Continued)

#26. #25 AND #11	1,544
#27. #26 AND [humans]/lim	1,338

DATABASE SEARCHED: CINAHL

Period searched: 1982 to September 2017

Last searched: 11 September 2017

Items	N° records
S1. MH substance withdrawal syndrome OR TX (detoxifi* or desintoxi* or disintoxi* or withdraw*)	89414
S2. MH opium OR MH Poppy straw	483
S3. TX opium	1,892
S4. S2 or S3	1,892
S5. S1 and S4	452
S6. PTrandomized controlled trial OR PT controlled clinical trial OR TX randomized OR TX placebo OR TX drug therapy OR TX random* OR TX trial OR TX groups	1,904,937
S7. S5 and S6	399
S8. S7 Limiters – Human	133

DATABASE SEARCHED: PsycINFO (OVID)

Period searched: 1887 to September 2017

Last searched: 11 September 2017

Items	N° records
1. detoxification.mp. or exp DETOXIFICATION/	3828
2. drug withdrawal.mp. or exp Drug Withdrawal/	7947
3. (detoxify* or desintoxi* or disintoxi* or withdraw*).tw.	36939
4. 1 or 2 or 3	40275
5. opium.tw.	608

(Continued)

6. poppy straw.tw.	3
7. 5 or 6	610
8. 4 and 7	72
9.exp INTERVENTION/	87650
10. exp Drug Therapy/	132461
11. exp Clinical Trials/	10542
12. exp Treatment Effectiveness Evaluation/	21886
13. (randomized or placebo or drug therapy or random* or trial or groups).tw.	648402
14. 9 or 10 or 11 or 12 or 13	802319
15. 8 and 14	29

DATABASE SEARCHED: the Cochrane Central Register of Controlled Trial (CENTRAL)

Last searched: the Cochrane Library 2017, Issue 9

Items	N° records
#1. MeSH descriptor Substance Withdrawal Syndrome explode tree 1	1,860
#2. MeSH descriptor Metabolic Detoxication, Drug explode tree 2	87
#3. (detoxifi* or desintoxi* or disintoxi* or withdraw*):ti,ab,kw in Trials	25,120
#4. (opium):ti,ab,kw in Trials	173
#5. MeSH descriptor Opium explode all trees	92
#6. (poppy straw):ti,ab,kw in Trials	0
#7. #1 OR #2 OR #3	25,185
#8. #4 OR #5 OR #6	173
#9. #7 and #8	29

DATABASE SEARCHED: The Index Medicus for the Eastern Mediterranean Region (IMEMR)

Period searched: 1984 to September 2017

Last searched: 13 September 2017

Note: In this database there was index terms which is different from Mesh heading in MEDLINE. After searching opium as index word in avdanced search option, we found only 181 studies. So, we just searched opium, which was the most relevant words in our search strategy.

The Search strategy:

opium [KeyWords] or opium [Title] or opium [Subject]

Retrieved records: 181

DATABASE SEARCHED: Barakat Knowlege Network System [Former Iranmedex (http://health.barakatkns.com)

Period searched: up to September 2017

Last searched: 13 September 2017

We searched the database for “opium” in English OR “teryak” in Persian. Opium in farsi is called “Teryak” and was written «تریاک».

Retrieved records: 1,322

DATABASE SEARCHED: Iranpsych (http://iranpsych.tums.ac.ir/)

Period searched: up to March 2012 (the database has not been updated since March 2012)

Last searched: 17 March 2012

We searched the database for “opium” in English OR “teryak” in Persian. Opium in farsi is called “Teryak” and was written «تریاک».

Iranpsych contain papers published in scientific journals, theses and conference proceedings. There three independent search box for these information. So, we searched the databases independently. The database has not been updated since 2012.

Databases for Papers Published in Scientific Journals: 185 records retrieved

Databases for Theses: 67 records retrieved

Databases for papers presented in seminars: 11 records retrieved

Main electronic sources of ongoing trials:

ClinicalTrials.gov register (http://clinicaltrials.gov/)

Last searched: 13 September 2017

We just searched “opium or (poppy straw)” in this databases.

Retrieved records: 18

The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)(http://apps.who.int/trialsearch/)

Last searched: 13 September 2017

We just searched “opium or (poppy straw)” in this databases

Retrieved records: 47

CenterWatch Clinical Trials Listing Service

Last searched: 22 September 2017

We chose all clinical trial which was classified as “Clinical Trials in Substance Abuse” or “Clinical Trials in addictions”. Total numbers of clinical trial found in this database were 23 studies. “Opium” as a key word was also searched and no result was found.

ISRCTN registry (http://www.isrctn.com/)

Last searched: 13 September 2017

We just searched “opium or (poppy straw)” in this databases.

Retrieved records: 2

Table: Number of retrieved studies by source

Databases	Date of searching	Total retrieved studies
This table was corrupted, and had to be replaced.		
MEDLINE	13 Sep 2017	95
Embase	13 Sep 2017	1,338
CINAHL	11 Sep 2017	133
PsycINFO	11 Sep 2017	29
CENTRAL	26 Sep 2017	29
IMEMR	13 Sep 2017	181
Iranmedex	13 Sep 2017	1322
Iranpsych	17 March 2012	185 (in Papers Published in Scientific Journals) 67 (in theses) 11 (papers presented in seminars)
ClinicalTrials.gov register	13 Sep 2017	18
The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).	11 Sep 2017	47
CenterWatch Clinical Trials Listing Service	22 Sep 2017	23
ISRCTN registry	13 Sep 2017	2

Appendix 2. Criteria for 'Risk of bias' assessment

Item	Judgement	Description
1. Random sequence generation (selection bias)	Low risk	The investigators describe a random component in the sequence generation process such as: random number table, computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots, and minimisation.
	High risk	The investigators describe a non-random component in the sequence generation process such as: odd or even date of birth, date (or day) of admission, hospital or clinic record number, alternation, judgement of the clinician, results of a laboratory test or a series of tests, and availability of the intervention.
	Unclear risk	Insufficient information about the sequence generation process to permit judgement of low or high risk
2. Allocation concealment (selection bias)	Low risk	Investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: cen-

(Continued)

		tral allocation (including telephone, web-based, and pharmacy-controlled randomisation), sequentially numbered drug containers of identical appearance, and sequentially numbered, opaque, and sealed envelopes.
	High risk	Investigators enrolling participants could possibly foresee assignments because one of the following methods was used: open random allocation schedule (e.g. a list of random numbers), assignment envelopes without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered), alternation or rotation, date of birth, case record number, any other explicitly unconcealed procedure.
	Unclear risk	Insufficient information to permit judgement of low or high risk. This is usually the case if the method of concealment is not described, or not described in sufficient detail to allow a definitive judgement.
3. Blinding of participants and providers (performance bias), objective outcomes	Low risk	No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding. Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
4. Blinding of participants and providers (performance bias), subjective outcomes	Low risk	Blinding of participants and providers ensured and unlikely that the blinding could have been broken.
	High risk	No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding. Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
5. Blinding of outcome assessor (detection bias), objective outcomes	Low risk	No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding. Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
6.Blinding of outcome assessor (detection bias),	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

(Continued)

subjective outcomes	High risk	No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding. Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear risk	Insufficient information to permit judgement of low or high risk
7. Incomplete outcome data (attrition bias), for all outcomes except completion of treatment	Low risk	No missing outcome data. Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias). Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size. Missing data have been imputed using appropriate methods. All randomised participants are reported/analysed in the group to which they were allocated by randomisation irrespective of non-compliance and co-interventions (intention-to-treat).
	High risk	Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups. For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate. For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size. 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
	Unclear risk	Insufficient information to permit judgement of low or high risk (e.g. number randomised not stated, no reasons for missing data provided; number of dropouts not reported for each group)
8 Selective reporting (reporting bias)	Low risk	The study protocol is available, and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way. The study protocol is not available, but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).
	High risk	Not all of the study's prespecified primary outcomes have been reported. One or more primary outcomes is reported using measurements, analysis methods, or subsets of the data (e.g. subscales) that were not prespecified.

(Continued)

		One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect). One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study. There are clear errors in reporting.
	Unclear risk	Insufficient information to permit judgement of low or high risk

CONTRIBUTIONS OF AUTHORS

Afarin Rahimi-Movaghar, Masoumeh Amin-Esmaeili, and Reza Yousefi-Nooraie developed the draft of the protocol. Masoumeh Amin-Esmaeili and Leila Hoseinie performed the electronic searches. Afarin Rahimi-Movaghar and Leila Hoseinie contacted study authors for missing data. Masoumeh Amin-Esmaeili and Jaleh Gholami inspected the titles and abstracts of the retrieved records for potential relevance, and Afarin Rahimi-Movaghar and Jaleh Gholami evaluated the full-text versions of the study reports for inclusion in the review. Afarin Rahimi-Movaghar, Reza Yousefi-Nooraie, and Jaleh Gholami developed the data extraction form. Jaleh Gholami, Masoumeh Amin-Esmaeili, and Afarin Rahimi-Movaghar assessed studies and extracted data. Afarin Rahimi-Movaghar, Laura Amato, Jaleh Gholami, Masoumeh Amin-Esmaeili, and Leila Hoseinie prepared the draft of the review.

DECLARATIONS OF INTEREST

Afarin Rahimi-Movaghar has no conflicts of interest to declare.

Jaleh Gholami has no conflicts of interest to declare.

Laura Amato has no conflicts of interest to declare.

Leila Hoseinie has no conflicts of interest to declare.

Reza Yousefi-Nooraie has no conflicts of interest to declare.

Masoumeh Amin-Esmaeili has no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Tehran University of Medical Sciences, Iran.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No major change.

INDEX TERMS

Medical Subject Headings (MeSH)

Amantadine [therapeutic use]; Amines [therapeutic use]; Baclofen [therapeutic use]; Buprenorphine [adverse effects] [therapeutic use]; Clonidine [adverse effects] [therapeutic use]; Cyclohexanecarboxylic Acids [therapeutic use]; Gabapentin; Methadone [therapeutic use]; Opioid-Related Disorders [*drug therapy]; Opium [*adverse effects] [therapeutic use]; Randomized Controlled Trials as Topic; Substance Withdrawal Syndrome [*drug therapy]; Tramadol [therapeutic use]; gamma-Aminobutyric Acid [therapeutic use]

MeSH check words

Humans